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AN APPROACH TO THE ETIOLOGY, DIAGNOSIS AND MANAGEMENT OF PERIPHERAL ARTERIOSCLEROSIS (Arteriosclerosis Obliterans)

WILLIAM E. JAHSMAN, M.D.*

ETIOLOGY

Articles on arteriosclerosis, especially on the relationship between the disease and diet, are appearing in increasing numbers, both in lay and professional literature. No definite etiology has yet been established and hence no specific therapy can be prescribed, dietary or otherwise. The disease is currently believed to be a metabolic disorder, a disturbance of lipid metabolism, which by some obscure means leads to accumulation of cholesterol in the lining of the arteries. The latter process is only one phase of arteriosclerosis; namely, atherosclerosis. Gofman[1,2] says that atheroma formation has two major features: 1) a definite focal character of the lesions and 2) an abnormality in the serum lipids associated with the development of the disease. He states further that the most plausible concept of the pathogenesis of arteriosclerosis is that certain circluating lipids are deposited and retained in susceptible focal areas.

The role of obesity in arteriosclerosis has been discussed by many writers, including Dublin and Marks[3], Gofman[1], and Gofman and Jones[4]. However Keys[5] is most emphatically positive about the direct relationship, neither including nor excluding the aging factor. He has shown statistically that there is an increasing incidence of fatal atherosclerosis in people who are overweight and that during periods of semi-starvation, deaths from vascular disease declines. In autopsy cases, the severity of atherosclerotic vascular degeneration was directly related to the degree of fatness of the whole body. He believes that though atherosclerosis has not been proved to be due to eating fat or cholesterol and probably is not due only to dietary factors, yet substantial control of atherogenesis may be achieved by avoiding excessive calorie intake and obesity and by limiting the fat content of the diet so that the extractable fats provide almost 25 to 30 per cent of the total calories.

Steiner, Kendall and Mathers[6] found serum cholesterol and serum lipid-phosphorus values elevated in patients with coronary artery disease as compared with a control group of apparently healthy normals. The increase in serum lipid-phosphorus was not proportional to the increase in serum cholesterol, resulting in an increase in the serum cholesterol-lipid-phosphorus molar ratio, which is of possible significance in atherogenesis.

Katz[7] says the basic tenet is that altered lipid-cholesterol metabolism is necessary for atherosclerosis to develop. Senescent changes in the artery wall are not considered of prime etiological importance. But Lansing[8] feels that the altered lipid-cholesterol metabolism concept is not entirely satisfactory. It does not explain the fact that some plaques are entirely fibrous and do not contain cholesterol. Neither does it explain the focal nature of arteriosclerotic lesions, the greater severity of lesions in the abdominal than the thoracic aorta, or the relative resistance of some arteries, such as the pulmonary, to plaque formation, and finally, it does not explain the connection between cholesterol metabolism and luetic aortitis or mitral stenosis, both of which are characteristically associated with severe arteriosclerosis. Lansing has shown quite conclusively that calci-

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fication of senescent tissue in the media of human arteries occurs with or without atherosclerosis and that elastic tissue changes begin as early as the third decade. When these changes and atheromatosis coexist, cholesterol accumulates in the intimal plaques *after* the underlying media has undergone elastic tissue calcification.

It would seem logical, then, to say that arteriosclerosis is a dual process: 1) aging of the arterial wall, establishing a substrate for 2) penetration and accumulation of cholesterol. It is possible that without such changes in the artery wall, whatever the factor or factors that condition the age change, cholesterol will not accumulate in the lining of the arteries. We cannot but agree with Moschowitz[9] when he says, "Arteriosclerosis is a compensatory reaction to normal arterial pressure which we cannot escape. Hence, it is the inevitable destiny of all animals (humans included) that possess a vascular system and live long enough."

DIAGNOSIS

There should be little trouble in the diagnosis of peripheral arteriosclerosis (arteriosclerosis obliterans) if an accurate history is obtainable. We know of no other condition that produces calf-muscle pain in one or both legs which comes on only with walking or other leg strain and disappears with rest. If similar pain involves the muscles of the thigh and hip, either alone or in addition to leg muscle pain, then segmental occlusion of larger arteries, femoral or iliac, must be thought of, either alone or together with occlusive arterial disease more distally.

What can be seen and felt on examination of the extremities is of next importance. With practice one becomes proficient at estimating the degree of arterial occlusion from palpation of the major arteries of the extremities. This must always be judged in connection with the history and other findings, since one or more of the pulses in the feet or at the wrists may be absent in a fair percentage of normal people. For the upper extremity, the Allen test will determine whether there is impairment of flow in radial or ulnar arteries. Even with palpable pulses in major foot or wrist arteries, smaller vessels may be narrowed or occluded and permit actual gangrene or ulceration of the part supplied by such distal branches. Skin color often gives helpful information. Increased blanching on elevation of the legs and red or bluish discoloration on dependency are characteristic of leg artery insufficiency. Frequently there is decreased temperature of the skin of the extremities, slow nail growth or transverse ridges on the nails.

Laboratory aids are often used to help in diagnosis. X-rays for blood vessel detail may show calcification, at least helping to exclude thromboangitis obliterans in a borderline case. It should always be remembered that calcification of the artery wall is no indication of the degree of arterial impairment and that failure to visualize calcium does not rule out arteriosclerosis or arterial insufficiency. In a recent series of 54 patients with arteriosclerosis obliterans, 32 had x-rays of the legs. Twenty-three were positive, 9 negative for calcium deposits in the artery walls. The age range for the positive cases was from 49 to 72 years and for the negative ones from 46 to 62 years. There was no direct relationship between the degree of calcification or its absence and the intensity of symptoms, nor was the degree of calcification related to age.

Aortograms and femoral arteriograms are being done quite routinely now to de-

tect the cases of segmental occlusion in the larger arteries of the lower extremities. The histamine-fluorescin test at times aids in deciding the site for amputation. Oscillometry is often done but seems of little value over palpation for pulses. Vasodilator tests are used regularly and give much help. In our experience, Priscoline intravenously (50 mgms.) has proven very satisfactory in most cases. When clinical findings are not corroborated by the results of dermatherm study with this drug, the temperature readings are repeated with lumbar sympathetic block or spinal anesthesia. These studies are carried out under constant temperature conditions, of course.

MANAGEMENT

Regardless of the controversies as to etiology, the fact remains that with the increasing number of men and women living to and beyond three score years and ten, physicians of today are faced with arteriosclerosis as the leading disease of the age. It naturally follows that there will also be more patients with arteriosclerosis of the extremities. Some will have symptoms and come for help. As already stated, no specific treatment is known. We cannot be as optimistic as those who feel that diet alone or a new vasodilator drug is the answer. But neither can we agree that little or nothing can be done once the disease blocks or narrows the lumen of the peripheral arteries. There must be a mid-way program, not *specific* therapy, but a plan of management which will effect an increased blood supply to an extremity with partially obliterated arteries.

To begin with, as Duryee[10] says, each case presents a different set of problems which must be managed from the standpoint of the patient's general condition and from proper evaluation of the actual vascular changes in the extremities. Certainly no one vasodilator drug will be effective in every case. Neither will sympathectomy be regularly advised or helpful. The plan of management should be for the patient as a whole, not just for the offending extremity.

It is inescapable that there will be some patients with sudden occlusion of one or more larger leg arteries with resultant severe pain, gangrene or other complication requiring major surgery, such as amputation. Thrombosis is more likely to occur in arteries with atheromata and calcification. It is the dreaded and important complication in arteriosclerosis. Fortunately, however, most patients with peripheral arteriosclerosis come to us when still ambulatory, with no or only minor complications, such as small ulcers or minimal gangrene. Even these require careful cooperation of internist and surgeon, so that the unfortunate few requiring necessary major surgery, may have it carried out without prolonged suffering. But the large majority will respond to conservative measures, for which we make a plea. These include the following:

1. Teaching patient and family the nature of his disease. Then he and they will appreciate the importance of the time element for improvement, which is always slow. It will mean for patience and better cooperation.

2. Training the patient and his family in good extremity care. Daily foot baths followed by cautious drying and application of foot powders lessen the chance for fungus infection. If the skin is dry or scaly, lanolin or other skin oil may be applied. Corns, callouses and other foot disorders should never be self-treated. Trauma of any type should be avoided. Soft, closely woven stockings and well-fitting shoes will tend to

reduce the danger of irritation and will keep the skin warm. In colder weather, whole body warmth is important, meaning long underwear, wool socks and other appropriate clothing.

3. New habits of activity. If there is much pain, or there are small ulcers or gangrene, hospitalization or at least rest at home for two or three weeks is often necessary. When again ambulatory the patient should know that some walking or other activity is actually helpful in promoting collateral circulation. But he must learn to walk slowly and only short distances, keeping activity just under the point of pain. Buerger exercises and contrast bath followed by gentle massage to the legs are also recommended, not only for the slight help this may give but also to bolster the patient's morale; he is doing something for himself.

4. Diet. Though there is no conclusive evidence that excess fats are a definite etiological or aggravating factor in arteriosclerosis, it is important to control weight. The best way to correct obesity is through a low fat diet and this. then, also controls the possible damage from excess lipids. But this does not mean the extremely low fat diets often prescribed which, in our opinion, are as crippling as the rice diet of Kempner. We cannot agree with Keys[5] that butter, cream, oleomargarine, salad oil, mayonnaise, fried foods, gravy, ice cream, chocolate and pastry containing shortening should be prohibited. The diet should be low in fat, but can still be palatable, attractive and balanced.

5. Preventing vasoconstriction. This means absolutely no tobacco and no vasoconstrictor type of drug. It necessitates avoiding chilling, not only of the extremities but also the body generally. Finally it requires control of nervous tension, anxiety, fear, anger or other emotional disturbances which are always aggravating factors.

6. Promoting vasodilation. Alcohol is without doubt the best vasodilator. But it must be prescribed with caution, as a medicine only, and preferably not more than an ounce of whiskey, or its equivalent in other alcoholic beverages, three times daily. If dermatherm study with intravenous Priscoline reveals residual arterial elasticity with a skin temperature rise of two or more degrees centigrade, this or other vasodilator drugs by mouth have some value. A new preparation, Arlidin, is reported to be the most satisfactory for dilatation of the deeper muscle arteries. Intra-arterial histamine has been lauded as a limb-saver by Mufson[11], but our limited experience with this drug has not been encouraging. It carries with it the danger of local arterial thrombosis or thrombophlebitis.[12] Sympathectomy in selected cases gives added warmth to the skin and is especially helpful in patients who suffer from coldness and superficial ulceration. It should not be expected to relieve pain.

7. The use of mechanical aids. Various types of physical and mechanical therapy have been used and at times are helpful. Buerger exercises and massage have already been mentioned. Dry and moist heat must be used cautiously to avoid burns. Tissue with impaired circulation does not tolerate either extreme of temperature well. The safest measure is a light warm blanket wrapped around the extremity and covered with a loose cottton boot to retain natural body heat. A heat cradle with the thermostat at 92 to 96 degrees Fahrenheit may be placed over the involved extremity. Reflex heat from diathermy over the sacral area is often comforting. If there are no

open lesions, Sitz baths may be used, 20 to 30 minutes, with the temperature of the water at 94 to 100 degrees Fahrenheit. For open lesions, moist compresses of warm normal saline solution for an hour three times daily are soothing and cleansing. Any preparation that irritates or increases pain should be strictly avoided. Without doubt the oscillating bed is the most helpful mechanical device. Patients with quite severe pain have been known to fall asleep on these rocking beds when many other attempts at producing comfort have failed. We have seen little help from venous compression, alternate suction and pressure and other mechanical aids so often recommended by the manufacturers of expensive apparatus.

8. Adequate treatment of other associated diseases, such as diabetes, osteoarthritis, blood dyscrasia, diseases of the spinal cord, vitamin deficiency, endocrine dysfunction or orthopedic defects.

In the previously mentioned series of 54 patients followed from 2½ years to 5 years, 36 had conservative medical treatment only. None developed complications and only two failed to respond satisfactorily. Both of these refused to stop tobacco. Of 12 who had medical therapy and sympathectomy, three continued to have pain and other untoward symptoms. All three also continued smoking. The remaining six were quite advanced cases for whom sympathectomy was advised in the hope of avoiding amputation but later required radical surgery because of unbearable pain and advancing gangrene. Three required unilateral supracondylar amputation and are doing well with prosthesis. Two had bilateral amputation but are also comfortable now and continuing some gainful occupation from a wheelchair, three years postoperatively. The final patient who had a cerebrovascular accident and a coronary occlusion one year before the final admission, got no help from sympathectomy and expired of a second coronary occusion following amputation of the involved leg.

Analysis of these three groups shows no significant difference in age range except that the six requiring amputation were 55 years or over. It was interesting, too, that the three patients who continued to have pain and other symptoms after sympathectomy were 46, 48 and 49 years of age.

SUMMARY

There is still no definitely known etiology for arteriosclerosis but it seems reasonable to say that it is the result of a dual process; namely, 1) aging of the arterial wall, establishing a substrate for 2) penetration and accumulation of cholesterol from a disturbance in lipid metabolism. The disease is doubtless present in every human who lives long enough but produces symptoms only in those who do not develop adequate collateral circulation to compensate for occlusion of the original vessels. There will always be some with sudden occlusion of a major artery, with ulceration or gangrene following trauma, or with segmental occlusion of a femoral or larger vessel, in whom the primary treatment will be surgical. But the majority of people with the disease will be ambulatory. For these a plea for conservative medical measures of therapy is made. Probably most important is the education of the patient and his family in an understanding of the nature of the disease so that there will be patience and cooperation. There are no miracle drugs, special diets, or gadgets that mean for quick recovery. There is only *control,* not *cure.*

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SYMPOSIUM ON POSTMASTECTOMY LYMPHEDEMA OF THE ARM

Introduction

BROCK E. BRUSH, M.D., MODERATOR*

We have selected for discussion this morning lymphedema of the arm following mastectomy. The occurrence of this troublesome complication causes distress and disability on the part of the patient and concern to the surgeon. Dr. Geoghegan will report some historical facts about this condition. Dr. Block will report the history and findings of the patients recently seen in the clinic. Since x-ray therapy has frequently been blamed for swelling of the arm, I have asked Dr. Eyler, Chief of the Department of Radiology, to present his views on this aspect of the subject.

We have this past year been using a device to give relief to patients with a large painful arm. It consists of (1) a sleeve, woven of special material in which two inflatable rubber tubes are incorporated (Fig. A), (2) a machine to produce inflation of the tubes for periods of 15 seconds each minute. We have used this apparatus on eleven patients and have been satisfied with the results. It is important that the device be used for 7-8 hours a day for the first few days of treatment. An elastic sleeve is worn between treatments.

Dr. Long of the Department of Physical Medicine is interested in this problem, especially in the field of prevention. Dr. Long will give us his views on this subject.

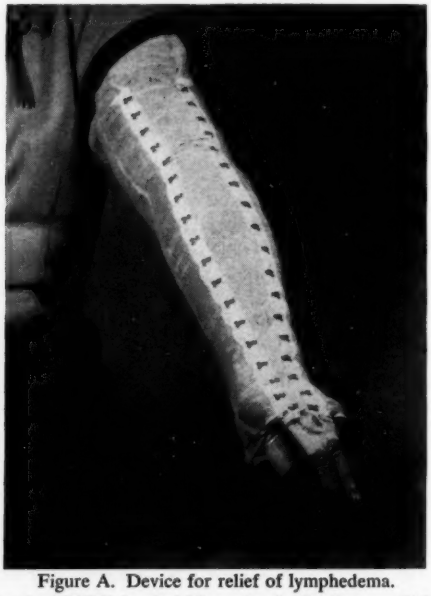

Figure A. Device for relief of lymphedema.
(Supplied by the JOBST Applied Biomechanics Institute — Toledo, Ohio.)

*Department of General Surgery

Postmastectomy Lymphedema of the Arm: Historical Review

THOMAS GEOGHEGAN, M. D.*

In his paper dealing with postmastectomy lymphedema Halsted[1] recounted his first experience with edema of an area following extirpation of the lymph nodes draining it. A patient operated upon in 1882 sustained tremendous edema of the scrotum after excision of his inguinal nodes. Halsted was again faced with this complication when he began to perform the radical operation for cancer of the breast. In reviewing his difficulties with this complication, which he termed "elephantiasis chirurgica", he concluded that infection was an invariable factor in its production.

In spite of newer methods for combating bacteria the incidence of edema of the arm after mastectomy remains high. Sampson Handley[2] in 1908 stated that "the brawny arm occurs in about one case of every six". In 1949 Lobb and Harkins[3] placed the figure at 80 per cent in a carefully studied series of 81 patients. In 31 per cent the edema was less than 1:5 cm.; in 27 per cent between 1.6 and 2.9 cm. and in 22 per cent greater than 3.0 cm. These workers incriminated postoperative radiotherapy as a causal factor.

Aside from the factors of infection and radiotherapy, which most workers do not believe to be of primary importance, venous obstruction and lymphatic obstruction have been singled out for consideration. Veal[4] demonstrated an increase in the venous pressure of the swollen arm together with venographic findings of partial or complete obstruction of the axillary and subclavian veins. The obstruction in most cases resulted from benign scar formation. Devenish and Jessop[5], on the other hand, could find little in the way of venous pressure changes, but showed pathologic detours in the lymphatic drainage routes in lymphatic dye studies.

The multitude of therapeutic suggestions for this complication have been outlined by various authors. Foley[6] has catalogued the conservative measures such as massage and the use of diuretics. Treves[7] discusses the many surgical procedures which have been used such as the Kondoleon procedure and axillary vein resection.

Some of these points will be amplified by the discussion which follows.

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Lymphangiosarcoma Occurring in Postmastectomy Lymphedema

MELVIN A. BLOCK, M. D.* JOSEPH L. FLEMING, M. D.**
JAMES R. GISH, M. D.***

One of the rare complications of lymphedema of the arm following radical mastectomy is lymphangiosarcoma. This lesion was first described in 1948 by Stewart and Treves[1] with a report of six cases. The authors noted that the condition had usually been considered to be Kaposi's sarcoma or cutaneous metastases of breast carcinoma previously. At least sixteen cases of this malignancy have now been reported, according to Marshall[2].

Lymphangiosarcoma in postmastectomy lymphedema occurs usually in arms that became edematous early in the post-operative period, although in the one patient with

this condition that we have seen the edema was not noticed until six years following surgery. The malignancy appears late post-operatively, six to twenty-four years later in reported instances. There has been no relation between occurrence of the lesion and the presence of metastases from mammary carcinoma in axillary lymph nodes. There is no relation either between occurrence of the lesion and the administration or lack of administration of radiation therapy for the breast carcinoma.

The appearance of the lesions of this malignancy are quite characteristic. They appear as purplish-red, subdermal, slightly raised lesions usually occurring in the arm. Satellite lesions appear and all may become confluent and become large lesions. Later the overlying skin ulcerates and serous or serosanguinous fluid along with necrotic malignant tissue may discharge. Thus, there is no good resemblance between this malignancy and recurrent mammary carcinoma. Lymphangiosarcoma occurring in postmastectomy lymphedema does not occur initially in the axilla and can be distinguished from malignant lymphangioma occurring in the axilla following radiation therapy to the axilla after radical mastectomy. Lymphangiosarcoma lesions enlarge and metastasize to the skin of the upper extremity, shoulder, chest and to the lungs.

Microscopic studies of biopsies may be misleading and the lesions may be reported as lymphangiectasis and benign inflammatory conditions. However, the diagnosis can nearly always be made from the history and gross appearance of the condition.

Treatment in general has been unsatisfactory. Radiation therapy and forequarter amputation individually or in combination have been used and yet the outcome has been fatal in nearly all cases. Rawson and Frank[3] did report a case in which a good response was obtained from radiation.

We have observed the occurrence of lymphangiosarcoma in post-mastectomy lymphedema in one patient. In this patient lymphedema was noted about six years postoperatively with the lymphangiosarcoma appearing eight years postoperatively. Forequarter amputation combined with radiation therapy was advised and this was carried out elsewhere.

Why lymphangiosarcoma occurs in chronic lymphedema of the arm is an interesting problem but entirely speculative.

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Postmastectomy Edema of the Arm: Roentgen Aspects

JAMES R. GISH, M.D.*
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This problem is encountered quite frequently in the patients seen in radiotherapy, usually it is difficult to determine the main factor that is causing the edema of the arm. There are at least four possible causes for this condition:

1. Radical surgery with disruption of the normal circulatory channels.
2. Radiation therapy with resultant delayed formation of lymphatic channels, scar formation, and slow healing.

3. Infection and/or fat necrosis in the operative wound with marked delay of formation of lymphatic channels.

4. Axillary metastatic disease with occlusion by pressure or invasion of the normal circulatory channels.

The patients usually have had radical surgery and appear to be well healed without infection, but underlying fat necrosis may be present, and certainly the majority have metastatic axillary disease. Only rarely does this condition develop in the arm when radiation therapy alone is used. It is more common for this condition to be aggravated while under treatment or immediately thereafter than to see it initiated during this same period. Some patients with far advanced cancer of the breast and obvious axillary metastases who have had no previous treatment of any kind show marked edema. However, many such patients show no edema.

The literature on this subject cites various conclusions regarding the relative importance of the major factors causing postmastectomy edema of the arm. Reichert[1] working with Halsted in the early twenties showed in animal experimentation that no significant edema occurred in the extremities of dogs when the soft parts with the exception of the artery, vein, and nerve were severed, provided that there was no infection in the wound. Veal[2] in 1937 concluded that occlusion of the axillary vein played a most significant part in causing edema of the arm. Holman, McSwain, and Beal[3] in 1944 after analysis of a hundred cases thought that infection and radiation therapy were the two most significant factors producing edema of the arm.

MacDonald[4] decided that resection of the axillary vein enabled him to perform a more thorough dissection of the axilla and also seemed to lower the incidence of postoperative edema, a direct contradiction of the opinion stated above. Deaton and Bradshaw[5] in a study of twenty-four cases concluded that the only common denominator in their cases of postmastectomy edema was infection in the operative wound.

In conclusion, there are at least four major contributing causes of this condition. Separating them in regard to their importance in a given case is quite difficult and sometimes impossible. In our experience, radiation therapy very infrequently initiates this condition, but occasionally does aggravate it. The timing of the appearance of the edema and the administration of the radiation therapy is the principal evidence supporting this opinion. Radiation therapy has little to offer in the treatment of this condition, except when caused by metastatic axillary disease alone.

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Physical Factors in Post-mastectomy Lymphedema

CHARLES LONG II, M. D.*

The major factors in the production of lymphedema in the post-radical mastectomy arm are failure of muscular pump and anatomic disruption of lymph drainage channels. The failure of the muscular pump action of the extremity takes place in three stages. First the arm is necessarily immobilized in the immediate post-operative period. During

this stage normal muscular action of the arm, particularly the shoulder girdle musculature, is prohibited. The second stage, disuse atrophy, occurs if immobilization is continued beyond a few days. In the final stage the patient may develop a frozen or partially limited shoulder, further inhibiting the use of the extremity and contributing further to the trend of disuse and hence failure of the muscular pump.

Actual interruption of lymph drainage channels through the axilla is probably the major cause of the lymphedema; however, cases can be cited in which the lymph vessels and nodes were relatively spared and yet lymphedema developed. Apparently both disuse and channel interruption factors are operative in most cases.

Physical treatment, prophylactic or definitive, is aimed at minimizing the effect of the two etiologic factors. Active motion of the shoulder should be initiated as soon as feasible post-operatively, certainly by the time the sutures are removed; partial range can often be prescribed safely a few days after operation, though full range exercises may have to be delayed.

The patient should be instructed during the further recovery period to exercise the arm with increasing frequency and increasing resistance, even with the use of some household articles (such as a flatiron) for weights. It has been shown that muscular activity is an efficient method of moving lymph from an extremity. This advantage is partially cancelled by the damming-up which may occur behind partially interrupted outflow channels.

The lymphatic blockage itself must be treated by methods designed to build up pressure in the lymphedematous extremity to the point where lymph is forced through the obstruction, dilating existing channels and perhaps forming collaterals. This can be done partially by active exercise, though this has the disadvantage of producing more lymph as it is forcing out existing amounts. Therefore, massage methods are often added in the treatment of the arm which is already lymphedematous. Massage can be taught to a member of the patient's family for home administration, or the patient may come to the physical therapist for treatment; in either case massage should be deep, should move from distal to proximal, and should be given daily.

Although there are discouraging reports in the literature concerning the use of mechanical constricting devices for the relief of edema, I have recently seen one particularly encouraging case in which the Brush[1] machine was used. This machine apparently builds up very high pressures and is kept on for long periods, possibly explaining the difference in results obtained here and elsewhere; further use and investigation with this device is indicated.

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SUBACUTE BACTERIAL ENDOCARDITIS

Medical Staff Conference

J. G. MATEER, M.D., Physician-in-Chief

Panel

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J. COLVILLE, M.D.*
E. H. DRAKE, M.D.**
E. GREEN, M.D.***
J. F. BRUNNER, M.D.****
H. H. GALE, M.D.****

Dr. Quinn: This morning we will present two interesteing cases and discuss some of the principles of diagnosis and results of treatment of bacterial endocarditis. Dr. Brunner will present the first case.

Dr. Brunner: A 16-year-old girl was admitted to the Henry Ford Hospital on August 17, 1955. She had experienced daily chills and fever associated with headaches, malaise, sore throat, nausea, and vomiting for eight days. Six days prior to admission she noted swelling and pain in the left ankle that persisted for four days. Five days prior to admission she noted a bluish tender area on the palmar surface of the tip of the left middle finger. She received an indefinite amount of penicillin both orally and by injection during the eight days prior to admission to the hospital. Her history revealed the presence of a heart murmur since an attack of rheumatic fever at the age of 11 years. In May and June, 1955, the patient was seen on two occasions with attacks of supraventricular tachycardia that subsided spontaneously. A diagnosis of inactive rheumatic heart disease with mitral stenosis and insufficiency was made at that time.

Physical examination revealed that her temperature was 41.2 C (106.2 F) and that the pulse rate was 120 per minute and regular. There were 20 respirations per minute, and the blood pressure 115/64 mm. Hg. She was a well-developed and well-nourished young female and appeared acutely ill. There was a single bluish tender lesion, 6 mm. in area and slightly elevated, on the tip of the left middle finger. Several palpebral conjunctival and subungual petechial hemorrhages were present. The heart was enlarged to the left, the point of maximal impulse being in the left sixth interspace 11.5 cm. from the midsternal line. The precordium was heaving, and a diastolic thrill was noted at the apex. A grade 4 harsh, high-pitched systolic murmur and an apical diastolic rumble were heard on auscultation. The spleen tip was palpable 4 cm. below the left costal margin. The remainder of the physical examination was negative.

Laboratory tests revealed that the hemoglobin level was 11.4 gm. per 100 cc.; there were 3,6000,000 red blood cells and 15,760 white blood cells per cubic milliliter. There were 73% polymorphonuclear leukocytes, 22% lymphocytes, and 4% monocytes. The sedimentation rate was 41 mm. per hour (Wintrobe), and the hematocrit was 37%. The urine was normal except for a trace of albumin. An electrocardiogram disclosed evidence

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of left ventricular enlargement. Cardiac fluoroscopy showed left auricular enlargement. Seven blood cultures taken on the third and fourth hospital days were all positive for an organism identified as Neisseria sicca. The organism was inhibited *in vitro* by 2.5 units of penicillin per cubic milliliter and by less than 0.56 units of penicillin combined with 5 mcg. of streptomycin per cubic milliliter.

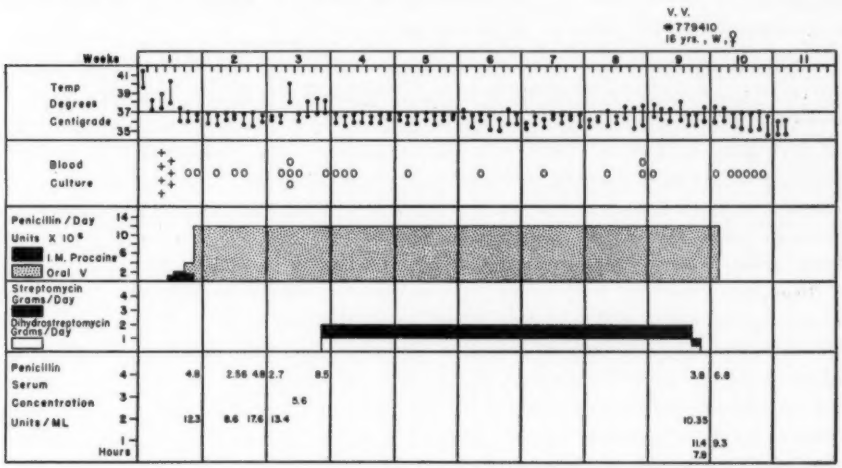

Figure 1

Course of patient with subacute bacterial endocarditis due to Neisseria picca (case 1.)

The patient's course is shown in the first slide (Fig. 1). On the fourth hospital day, intramuscular administration of one million units of procaine penicillin twice daily was started. On the sixth hospital day parenteral administration of penicillin was discontinued and oral administration of 2 million units of penicillin V every four hours was begun. Within 48 hours of the initiation of penicillin therapy the patient became afebrile and showed marked symptomatic improvement. The tachycardia decreased, and the systolic murmur decreased in intensity. On the 15th day of treatment she developed a headache and her temperature rose to 40.4 C (104.5 F). New petechial hemorrhages were noted on the soft palate and in the conjunctiva. During the ensuing four days her temperature remained elevated, although blood cultures obtained at this time were all sterile. The results of the in vitro sensitivity test became available at this time, and 0.5 gm. of streptomycin plus 0.5 gm. of dihydro-streptomycin given intramuscularly twice daily was added to the course of therapy. She promptly became afebrile, and no new petechiae were noted. The combined therapy was continued for six weeks. Frequent blood cultures during treatment and twice weekly for one month after treatment was discontinued were sterile. The patient was last seen 11 weeks after cessation of treatment and has maintained clinical and bacteriological remission.

Dr. Quinn: Dr. Gale will present the next case.

Dr. Gale: An 18-year-old man was admitted to the Henry Ford Hospital on September 14, 1955. Three and one-half weeks prior to admission he had developed a toothache and was found to have a deeply carious tooth, without evidence of apical abscess. He

was given 300,000 units of procaine penicillin G with 0.25 gm. of streptomycin sulfate and 0.25 gm. of dihydrostreptomycin sulfate one hour preoperatively, and the tooth was extracted. For the next 5 days, 200,000 units of penicillin G was given orally three times daily, followed by 200,000 units twice daily for 10 additional days. One week before admission he noted the onset of fever, with temperature of up to 39.7 C (103.5 F) accompanied by mild malaise. This persisted until September 12, when he presented himself to the outpatient clinic and a blood culture was drawn.

His history disclosed a known heart murmur since the age of 6 months. At the age of 10 he developed daily fever, with temperature ranging from 37.8 to 39.5 C (100 to 103F) and a cough that persisted for 10 months. He was first admitted to the Henry Ford Hospital on July 23, 1947, with this complaint. Numerous blood cultures were sterile. A diagnosis of bacterial endocarditis without bacteremia was made, and he was treated with 100,000 units of aqueous penicillin, administered intramuscularly every three hours for 50 days. He was asymptomatic until January 27, 1954, when he developed fever, chills, cough, and migratory arthralgia. Numerous blood cultures were sterile. A diagnosis of bacterial endocarditis without demonstrable bacteremia was made, and he was treated with 4 million units of aqueous penicillin and 1 gm. of streptomycin daily for four weeks. He became afebrile and asymptomatic. On April 10, 1954, he was admitted for the third time with recurrence of fever. Again blood cultures were sterile, and he received tetracycline orally for 21 days with prompt remission of fever. Data obtained from cardiac catheterization in January, 1955, were consistent with a diagnosis of infundibular pulmonary stenosis.

Physical examination revealed that his temperature was 40 C (104 F), his pulse rate 100 per minute, and respiration rate 24 per minute. The blood pressure was 110/70 mm. Hg. He appeared moderately ill with a flushed face. No petechial hemorrhages were noted. The heart was not enlarged to percussion. The rhythm was regular. A grade 4 harsh systolic murmur was audible along the left sternal border, loudest at the third left interspace. A systolic thrill was palpable in this area. The pulmonic second sound was absent. No diastolic murmur was heard. The spleen was not palpable.

Laboratory tests revealed that the hemoglobin level was 15.9 gm. per 100 cc., and there were 5,950,000 red blood cells and 9,700 white blood cells per cubic millimeter. There were 82% neutrophils, 12% lymphocytes, 5% monocytes, and 1% basophils. The urinalysis was negative. Roentgenogram of the chest disclosed slight prominence of the left cardiac border. Three blood cultures obtained during the first two days of hospitalization were positive for alpha-hemolytic streptococci. The organism was sensitive in vitro to 0.04 units of penicillin per cubic milliliter. The patient's course is shown in slide 2 (Fig. 2). He was given 2 million units of penicillin V orally every four hours for six weeks. His temperature fell to normal on the second day of treatment, and his symptoms subsided promptly. Biweekly blood cultures made during treatment and for one month after discontinuing therapy with penicillin remained sterile. The patient has been followed for three months since completion of therapy, and there has been no clinical or bacteriological evidence of relapse.

Dr. Quinn: These two cases present some of the usual but contrasting aspects of bacterial endocarditis. The first patient had pre-existing rheumatic heart disease, the second congenital heart disease. One presented with a three weeks illness with undiagnosed

fever and inadequate antibiotic therapy; the other presented with persistent fever following "adequate" chemoprophylaxis at the time of dental extraction. Classical signs of bacterial endocarditis i.e. splenomegaly, emboli; etc. were found in the patient with acquired heart disease but absent in the patient with the congenital cardiac lesion. Both patients, however, presented with persistant fever and in both multiple blood cultures were positive. Dr. Green would you comment further about these cases.

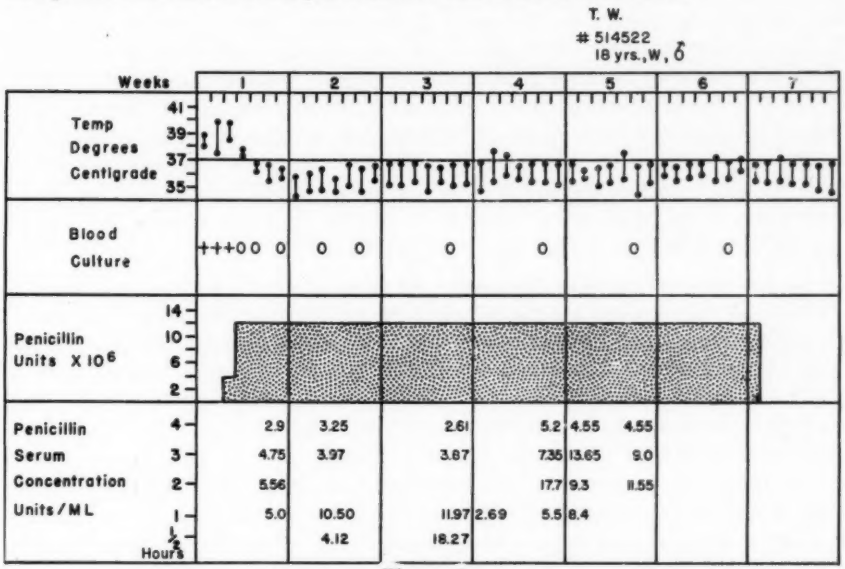

Figure 2

Course of patient with subacute bacterial endocarditis due to alpha-hemolytic streptococcus. (case 2.)

Dr. Green: The second case was of considerable interest in that this boy received quite adequate, or at least what we think is quite adequate, prophylaxis at the time of his dental extraction. This raises the interesting question, "Did his bacterial endocarditis exist prior to the dental extraction?" I am afraid that we do not know the answer to that. It is also of interest that this boy's pulmonary stenosis is infundibular in location in that it has previously been thought to be very rare for pulmonary stenosis to develop bacterial endocarditis unless it was valvular. However, we now have two cases of infundibular pulmonary stenosis who have had classical bacterial endocarditis so I do not think we can hold to this any more. The organism is of interest in the first case, in that Nisseria sicca is, certainly in our experience, a very unusual organism and I think that it was fortunate that we did have adequate penicillin sensitivity test.

Dr. Quinn: I think the panel will agree that Nisseria sicca is generally regarded as a non-pathogen and had we not had seven positive cultures and classical signs of bacterial endocarditis clinically, this organism would be open to question as a cause of this patient's illness.

Another contrasting point in these two cases relates to the sensitivity of the organism. The Nisseria sicca was inhibited *in vitro* by the tube dilution method by 2.5 units of penicillin per cubic milliliter. Later when we conducted *in vitro* test with a combina-

tion of penicillin and streptomycin the organism was inhibited by less than 0.5 units of penicillin combined with five micrograms of streptomycin. Thus, this would be classified as a moderately resistant organism. The streptococcus viridans isolated in the second case was sensitive *in vitro* to 0.04 units of penicillin per cubic milliliter.

I think this is the point to talk a little about prophylaxis with regard to dental extraction, as this point has been raised. It has been recommended by the Committee on Prevention of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association that one of the following two regimens of penicillin prophylaxis of subacute bacterial endocarditis be used in patients with rheumatic heart disease or congenital heart disease at the time of dental extraction. The first dose schedule recommended is the injection of 600,000 units of aqueous penicillin G and one injection of 600,000 units of procaine penicillin in oil with 2% aluminum monosterate given 30 minutes before the dental extraction. The alternate plan consists of the administration of oral penicillin G, 250,000 to 500,000 units four times a day, for one day before and four days after the dental extraction.

It has not been established just what the value or risk of such a procedure is in a patient who has had this kind of treatment. In a patient with rheumatic heart disease or congenital heart disease, the likelihood of developing bacterial endocarditis after a single tooth is extracted is estimated to be about one in five hundred. This probably explains why an adequate study has never really been done to find out exactly what should be used. I think that most everyone agrees it is sound clinical judgment and theoretically correct to employ such prophylaxis. Exactly what durg to use or how long to use it or in what dosage has not, however, been established by adequate study. There are, interestingly enough, four reported cases of bacterial endocarditis following tooth extraction in which prophylactic antibiotic therapy was used. Three of these received small or moderate doses of penicillin and developed endocarditis despite this. The fourth reported case was treated more intensely with something like a million units of penicillin daily for six days. This patient's subsequent endocarditis proved to be due to a penicillin resistant organism. Thus, the possibility arises that if you treat too intensely and eliminate the sensitive organisms one may end up with endocarditis due to a resistant organism. I will ask each member of the panel what their current practice is on the prophylaxis of bacterial endocarditis.

Dr. Drake: At the present time, we believe that prophylaxis should consist of the following: In the first place, a quick-acting preparation such as Dr. Quinn mentioned should precede the actual extraction and then for at least four or five days following the patient should receive either orally or by injection, a penicillin preparation supplemented by streptomycin.

Dr. Green: Our practice is very much the same and I have nothing to add except that I think in prophylaxis of enterococcus endocarditis, we have felt it necessary to cover with larger doses of penicillin during times of therapeutic abortion or similar procedures in areas where the enterococcus is prevalent.

Dr. Colville: I think that we would agree with that method. The important thing to stress here is the fact that you cannot prevent bacteremia with prophylactic penicillin in one hundred per cent of the cases. You can cut it down but some patients will still develop bacteremia. Therefore, the only additional suggestion one might make is that

we continue the prophylaxis for approximately a week in the hopes that if these organisms find a suitable focus and begin to multiply, the penicillin will then be active. As you know, penicillin is not active against an organism that is not in the active growth phase.

Dr. Quinn: The next point which we would like to discuss in relationship to diagnosis is the matter of blood cultures. Just how many cultures should be taken, how long one should wait before treatment is started, etc.? I wonder if Dr. Colville would discuss this.

Dr. Colville: I think the point to stress about blood cultures is that multiple cultures are essential. A single blood culture on occasion may be more confusing than no culture. Supposing this single culture reveals an organism such as a coagulase negative staphylococcus? Normally this organism inhabits the skin and nasal mucous membranes and may be a contaminant in a blood culture. On the other hand, it may represent the offending organism in bacterial endocarditis. It is difficult to commit a patient to a long, strenuous, and expensive course of therapy on the basis of such tenuous evidence. If multiple cultures reveal the same organism, the evidence for treatment is much more secure.

How long should we delay before instituting therapy? In one series of 140 adequately studied cases, 90 per cent of the cultures that were positive occurred within the first three days of the disease, that is, after the patient appeared in the hospital, and only 1 per cent after the first five days. Therefore, one would think that if you are going to get positive blood cultures, you should in the vast majority of cases, get them within the first three days. I certainly do not think that there is much to be lost by delaying treatment for three to five days to get blood cultures, since such a delay does not alter the results of treatment.

Failures to obtain positive cultures may occur because of the lack of putting the blood into appropriate media, incubating the culture long enough and the actual technique of taking the culture.

With reference to multiple sites for blood culturing, I might say that as far as I am concerned, venous blood is apparently as good as arterial blood with the exception, and this is purely a personal experience, that bone marrow will occasionally give positive cultures when peripheral blood does not. I know Dr. Drake has a comment about arterial and venous blood cultures.

Dr. Drake: Yes, I would like to give what seems to be a minority opinion here in favor of arterial blood cultures. I have seen them successful in several instances that I can remember where the repeated venous culturing had failed. It seems to me that any capillary system will, to some extent, act as a filter and that theoretically, if not practically, the arterial blood culture should offer some advantage, and I believe does.

Dr. Quinn: Do we all agree that perhaps the bone marrow has its special value in patients who have had a dose or two of penicillin before we see them and we might be able to culture the organism there easier than out of the blood?

Dr. Drake: Yes, I would agree with that.

Dr. Quinn: I am sure we would all agree that if the patient has a cerebral hemorrhage or is in severe congestive failure, we should not wait the two or three days but we can then get 5 or 6 cultures in a few hours and proceed with treatment. Now let us classify

these organisms that are isolated according to their sensitivity. We will turn to Dr. Colville again and ask him also to discuss sensitivity tests in bacterial endocarditis.

Dr. Colville: I think at the onset the comment should be that all sensitivity tests are only rough guides. We all know of cases where we have *in vitro* a highly sensitive organism which does not respond satisfactorily to what would appear to be adequate antibiotic therapy. However, sensitivity tests are a guide and the accumulated experience enables one to predict the results of treatment with some degree of accuracy on the basis of these studies.

I would like to say something about methods first. I think that tube dilution methods are certainly the most accurate. Clinical experience in bacterial endocarditis has been correlated with the tube dilution inhibition study method rather than with the disk sensitivity which is the popular and easier method, and the one which is carried out in almost all hospitals. Tube dilution is an all or none response. The organism is either completely inhibited or it is not inhibited at all, as we read the tests. One gets a fairly accurate reading, can carry the dilutions down into very minute amounts and the end point is clear cut. With the disk sensitivity method as presently employed, one uses the filter paper disk which is saturated with antimicrobial agent and put on a plate. On the basis of the size of the zone of inhibition, a report of moderately or highly sensitive or resistant organism is made. This is a very crude index. Therefore, I would think that in subacute bacterial endocarditis, for accuracy's sake, we would want tube dilution studies in all of these cases. Secondly, with tube dilution methods one is able to do a synergism, antagonism and additive type of study. This is not possible with a disk system.

With reference to penicillin, I think one could say that organisms which are sensitive to less than 0.10 of a unit of penicillin per milliliter *in vitro* may be considered to be generally sensitive. Those from 0.1 to 0.9 of a unit are moderately resistant and one unit and above are highly resistant. With streptomycin, a sensitive organism is inhibited by less than 10 micrograms. With the tetracyclines, the evidence is quite confusing, but one would think that a sensitive organism is inhibited by less than 2 to 2.5 micrograms per ml. With bacitracin and erythromycins, I do not think that there is enough evidence accumulated to say what the sensitivity means.

Dr. Quinn: I think this point of tube dilution is most important. We first of all have to realize the practicality of this test, that is, to do tube dilutions on all specimens sent to the bacteriological laboratory would be an impossibility. Many hours are taken to do these tests. I certainly feel that in all cases of septicemia where documented clinical experience is available to guide your treatment by tube dilution sensitivity tests this is the only method one can rely on. We have felt that the disks sometimes were less than valuable, even misleading, i.e., in the second case presented the alpha streptococcus originally isolated was found to be only moderately sensitive to penicillin by the disk method but highly sensitive by the tube dilution method. In cases other than bacterial endocarditis, if one is well versed in the clinical experience with various antibiotics and what they can do, singly or in combination, one can frequently get along without sensitivity tests. I am not excluding them, but I think one must be very careful with interpretation of sensitivity tests especially if the disk method is employed. Dr. Green, do you have some comments in this regard?

Dr. Green: The only other comment would be that in certain cases of penicillin resistant organisms such as the enterococcus, I think it is a very wise idea, although it is a time consuming job for the laboratory, to set up combination sensitivities with penicillin and streptomycin in the same tube. We have found this extremely helpful in a number of cases with resistant organisms that look impossible to treat with penicillin alone but were sensitive to quite easily obtainable clinical level with the combination.

I think that it is important to remember that if you are dealing with an enterococcus you should use a combination of penicillin and streptomycin. This is true even if the tube dilution method shows a penicillin sensitive enterococcus. One can almost predict with assurity that treatment is going to fail if only penicillin is used unless you employ massive doses.

Dr. Quinn: The next step would seem to be to decide just what drug to use, and I think it is generally agreed that penicillin is the drug of choice in most cases of bacterial endocarditis. Secondly, the amount of penicillin given has to be large. Thirdly, the duration of treatment must be prolonged. I do not think anyone would disagree with these three points. There would be, however, some difference of opinion about just how much penicillin to use or just how long to use it, and we would like to explore this just a little bit. To approach this matter I will ask Dr. Drake to classify endocarditis according to what he might call sensitive and resistant forms, thinking not just of the causative organism but also of other things like duration if illness, etc.

Dr. Drake: Actually, we might define a resistant case of endocarditis as one which fails to respond in the expected manner to treatment. There are several factors which contribute to resistance. One of these is the long duration of the illness prior to diagnosis and therefore institution of therapy. This is quite important. Another, of course, is the isolation of a virulent organism or a resistant organism in the laboratory. Another factor is the failure to isolate any organism at all. In these circumstances, of course, there is a delay in the institution of the proper therapy. Still another factor is the presence of inadequate early attempted therapy which may sometimes turn a case into quite a resistant one from a therapeutic standpoint. Lastly we might mention the development of some complication during the course of therapy such as heart failure.

Dr. Quinn: Do you think that these factors have something to do with the dose and also with the duration that you would treat a patient?

Dr. Drake: Yes, I do, but only in a general way, in that they would tend to make one start out with adequate doses and continue the therapy for an extended period of time. The exact limits on that we will set later.

Dr. Quinn: Well, lets get into this matter of short term versus long term treatment. We will turn to Dr. Colville again and ask him to tell us a little about penicillin blood levels. Although these have been depreciated a certain amount, I think that perhaps they are rather important and give us some idea as to what dosage or what route of treatment we might employ.

Dr. Colville: The blood levels obtained with any penicillin agent depend upon the type of agent used, the amount given and the route by which it is given. To briefly summarize one could say that using crystallin penicillin intravenously one expects a very high peak

rapidly. This is achieved by giving a large intravenous dose over a short period of time. Studies in animals have indicated that if one gives a million units of penicillin intravenously in five seconds the blood level in the aorta at about 12-15 seconds will approximate about 200 or 300 units per cubic milliliter. There is a very rapid fall of the blood concentration, and at the end of an hour the levels will be below one unit.

When one gives penicillin by continuous intravenous drip, in contrast to the sudden peaking type of dose, one achieves a relatively constant level that will roughly approximate one unit in the serum for every million units given intravenously per 24 hours. Therefore, if we gave 24,000,000 units a day, we might expect a continuous level in the region of 24 units. This is provided, of course, that the patient has competent renal function and no blocking agent has been used.

Intramuscular crystallin penicillin produces a curve similar to the rapid intravenous route. The peak is reached in 15 to 20 minutes, with valves of 20 to 100 units after a large dose followed by a rapid fall to less than two units at the end of four hours. Parenteral repository forms such as aqueous procaine penicillin G or procaine penicillin G in oil give levels that never reach the high peaks of intramuscular or intravenous crystallin penicillin. With a 600,000 unit dose, the peak might be in the region of 5 to 10 units at the end of an hour. This falls off gradually, so that by 24 hours the penicillin is only just detectable in the serum.

Oral penicillin has been generally discouraged and I think for a very good reason. It has been shown that the absorption is erratic in that only 10-15% of crystallin penicillin G is absorbed from the gastrointestinal tract. However, it has been demonstrated that levels just as high as those from intramuscular, subcutaneous or any other parenteral route can be obtained if you use enough of this agent. More recently we have had experience that you have seen on these slides with penicillin V or phenoxymethyl penicillin. This agent is apparently better absorbed from the gastrointestinal tract and over longer periods of time. Based on what we know at present, about 30% or possibly 35% of this preparation is absorbed from the gastrointestinal tract, and we do get appreciable blood levels. These levels are somewhat in between those seen with intramuscular procaine penicillin G and intramuscular crystallin penicillin G in that we get the peak at about the same time, at a half hour to an hour, and obtain a level similar to that with procaine penicillin but we see a rapid fall off so that levels are down quite low at the end of four hours with this type of medication.

Dr. Quinn: To summarize and get the opinion of other panel members, it would seem to me that about 12,000,000 units of penicillin V orally in 6 divided doses daily will give us a level of around 8 units in the serum. About the same level would be obtained with 600,000 units of procaine penicillin intramuscularly every six hours. If you also give probenecide you will get levels about twice that high with either of these agents. This would be roughly equivalent to a continuous intravenous dose of about six to eight million units per 24 hours. It is a little hard to compare this with rapid intravenous or intramuscular crystallin penicillin because one gets a peak and it falls right off, but it would seem to me that about 500,000 units of aqueous crystallin penicillin G intramuscularly every three hours would simulate this dose. I would, therefore, propose the following four treatment schemes as equivalent for use in treating a sensitive or a moderately sensitive case of subacute bacterial endocarditis: Oral penicillin V, 12,000,000

units daily; aqueous procaine penicillin G 600,000 units every six hours; a continuous intravenous drip of 8,000,000 units of crystallin penicillin G per day; or, intramuscular administration of crystallin penicillin G, 500,000 units every three hours. Do the other panel members agree that these schemes are more or less equivalent?

Dr. Drake: Yes, I feel they are more or less equivalent. Most of our cases that Dr. Green and I have recently gone over, have been treated either with the intermittent intramuscular, using the doses that Dr. Quinn mentioned, or the continuous intravenous route employing approximately between ten and twenty million units a day. We have not in that scheme, routinely at least, employed anything extra to give peaks. We have attempted no treatment with the oral product.

Dr. Quinn: Do you feel these schemes are satisfactory for the resistant cases or do we have to give higher doses?

Dr. Drake: Well, that was for the sensitive cases. You would have to go higher with the resistant ones.

Dr. Quinn: Now having defined several dose schedules we should discuss the matter of duration of treatment. I would recommend to all of you an editorial in the July, 1955 issue of the American Journal of Medicine on the duration of treatment which we will not have time to cover, but certainly it is most important that you not stop treatment early. Giving a large dose over a short period will give you more treatment failures than giving smaller doses over a long period. In general, the sensitive cases are treated for two to four weeks with these dose schemes we have mentioned, and the resistant cases are treated for not less than six weeks with dose levels about two or more times greater than these. Now, I wonder about the importance of streptomycin routinely in these cases. Do you have any feelings about that, Dr. Colville?

Dr. Colville: I would differ a little in opinion here in that I think eight million units intravenously continuously would be a better dose than twelve million units intermittently orally. Since absorption of penicillin by the oral route is somewhat unpredictable, I think you would do better with the intravenous route unless you were prepared to do blood levels and make sure that adequate levels were being achieved with the oral medication.

If there is any evidence of resistance occurring during therapy or if the patient does not respond, then certainly streptomycin should be added. Otherwise, I should think that penicillin alone in a case due to sensitive organisms should be adequate.

Dr. Quinn: I think that a lot of people follow Dr. Hunter's and Dr. Dowling's recommendation that 600,000 units of aqueous procaine penicillin G four times a day along with streptomycin for two weeks will cure about 90% of cases due to streptococcus viridans. When dealing with an enterococcus and perhaps with most non-hemolytic streptococci one should use streptomycin along with the penicillin and continue treatment for four to six weeks. As an alternate plan with streptococcus viridans, penicillin alone is adequate but should be given for six weeks. Staphylococcal endocarditis poses many problems, and we will not have time to discuss treatment of this type.

Dr. Green and Dr. Drake have reviewed the Henry Ford Hospital experience and Dr. Green is going to briefly summarize this.

Dr. Green: We have available for study 61 consecutive cases of endocarditis since the advent of penicillin which we have been able to follow from 2 to 12 years. Of this group, there are 25 cases where recovery has been complete without any detectable aggravation of heart disease and these patients at the present time are virtually asymptomatic. These patients had a total of 28 episodes of bacterial endocarditis without any recurrences; that is, the three cases with a second attack were all reinfections. The following types of heart disease were observed; rheumatic occurred in 19 of these, of which 11 were mitral only, 5 were combined aortic and mitral and 3 were aortic alone. The 7 congenital heart cases included infundibular pulmonary stenosis, intraventricular septal defect and patent ductus. The most common organism was, of course, the penicillin sensitive or only slightly resistant type of streptococcus viridans and we had eighteen cases due to this organism; one enterococcus which was penicillin resistant *in vitro* to five units per cubic milliter; a penicillin sensitive staphylococcus occurred in 5 cases; and, we had 5 with negative blood cultures. In general, all the patients in this group had organisms for which appropriate levels could be reached clinically. One enterococcus was finally cured with one billion units of penicillin and streptomycin over a period of ninety days. As contrasted with the entire series, the congenital group seemed to do fairly well unless perhaps there was aortic valve involvement or a resistant organism.

We have a second group of ten patients who are symptomatically well but showed some residual effect such as progression of cardiac murmurs or something that was felt to be fairly definitely related to the bacterial endocarditis. We cannot be sure that these patients developed these findings on the basis of the bacterial endocarditis since the progress of rheumatic heart disease is such a variable thing. All of these cases were caused by streptococcus viridans which was more or less sensitive to penicillin, except one which had a negative culture and one enterococcus which was again only slightly sensitive to penicillin. The distribution of the structural heart disease in this group was entirely rheumatic except for one congenital aortic stenosis in which a murmur of aortic insufficiency appeared early in the course. There was one patient with no evidence of structural heart disease.

There are five patients in the third group who have survived the infection but are considerably aggravated. They have congestive failure or other fairly serious symptoms at the present time. Three of these cases were due to streptococcus viridans, one had a negative blood culture and there was one moderately resistant enterococcus. All had rheumatic heart disease, four with mitral involvement alone, and one with aortic stenosis.

Out of the total of 61 infections which we have followed, 21 patients have subsequently died. All of these had rheumatic heart disease except for one congenital bicuspid aortic valve with aortic insufficiency, one patient who had luetic aortitis with aortic insufficiency and one child with ventricular septal defect who had a resistant staphylococcus and developed a mycotic abscess at the root of the great vessels. A total of 10 of the 21 fatal cases had aortic valve involvement which may be of some importance. The following organisms were observed in the fatal group; streptococcus viridans in 8 cases; 3 were only moderately sensitive to penicillin and 5 were undetermined; enterococcus occurred in 3 cases; the staphylococcus occured in 6 cases. Interestingly enough in the staphylococcus group, 5 were penicillin resistant (in contrast to none in the non-fatal group) and the sixth fatal case was only slightly sensitive.

Nonhemolytic streptococcus occurred in 2 cases and 2 were blood culture negative.

Of this fatal group, 2 patients were terminal on admission and died in the first few days of treatment. The following causes of death were observed: early progressive cardiac failure with uncontrolled infection in 5 cases; progressive early heart failure with infection apparently controlled, 5 cases; subarachnoid hemorrhage with emboli, 2 cases, in one of which the infection in the heart was controlled; ruptured mycotic aneurysm, 2 cases; sudden death at 2 months with infection cleared, 1 case; uremia with infection cleared, 1 case; 1 incidental death of carcinoma of the kidney; and late congestive failure occurred in 3 cases.

In terms of our present knowledge, we felt that treatment was grossly inadequate in 6 cases but these occurred very early in the series after the introduction of penicillin. If we correct our mortality and eliminate all those patients who died after a year of freedom from symptoms and those who died within the first three or four days of hospitalization, our mortality is 21%.

From this data, we would have to conclude that resistant organisms present a most serious prognostic implication as well as advanced cardiac disease with failure and long continued advanced infection at the time of the diagnosis. In only six patients in this series was there evidence of failure to eliminate the intracardiac infection. However, the highest incidence of fatal complications occurred in this group where infection was more difficult to bring under control and progression of structural heart disease was more flagrant in this group.

Dr. Quinn: Dr. Drake would you discuss the several points the panel proposed just before this meeting?

Dr. Drake: One of the points you asked me to bring up was the question of relapse versus reinfection. Normally we arbitrarily set a time limit of one year. After one year we term a case a reinfection; before one year, a relapse. This is purely arbitrary and other people have selected time limits as short as two months. This presumes, however, that the same organism is involved. If a different organsim comes into the picture then it is a reinfection no matter when it occurs.

Also, you wish some clarification on acute versus subacute. Formerly, before penicillin, the acute bacterial endocarditis was defined, arbitrarily again, by a time limit of the duration of the infection, usually about six weeks. With the advent of the antibiotics, however, this became obsolete. Actually an acute endocarditis is merely a complication or an event occurring in the course of some other acute pyogenic infection, while subacute bacterial endocarditis is actually an entity in itself. In the acute form of the disease, you can usually recognize and locate the pyogenic focus. The organism is usually more virulent and there need not be any underlying heart disease.

Also, you asked me to bring up something in regard to fibrillation and congestive heart failure. There used to be an axiom that fibrillation and congestive heart failure do not occur, or occur only rarely in connection with bacterial endocarditis. Some even went so far as to say that the presence of one of the two complications mentioned was a protection against bacterial endocarditis. The first statement is true and the second is decidedly not so. It is true that the incidence of fibrillation and congestive failure

preceding bacterial endocarditis is low. It is quoted in the literature as being about three per cent. I think our series ran about ten per cent, but there is no protection offered by the presence of fibrillation. Actually what happens is something like this — in the course of rheumatic heart disease, the individual has recurrent episodes of thrombotic vegetations which are usually non-infected and which heal in the course of time. Actually, with the frequent occurrence of transient bacteremia which we know occurs, it is a wonder that they do not get infected more often and there must be here some host factor which protects the individual. With repeated healing, there comes increased scarring of the valves and progression of the rheumatic disease. Now, fibrillation, by and large, is a manifestation of an advanced rheumatic heart disease, and when this stage is reached the individual in the main has demonstrated his ability fairly well to resist infection of his vegetations. There are exceptions, of course, and these exceptions represent ten per cent of our series.

Dr. Quinn: Now just to go back to the two cases which were presented this morning. The second case is certainly a patient with a sensitive organism with none of the complications, who clinically was in the sensitive group and who responded very nicely to penicillin alone in the average dose which we mentioned over a period of six weeks. The first patient was complicated in that she had a resistant organism. She had had almost a month, of antibiotic therapy before she was admitted. She had an unusual organism. She had had several bouts of fibrillation. She suffered relapse clinically, and it was necessary to use a combination of penicillin and streptomycin in this case.

I would like to close the panel discussion by asking how we can improve our results even above the corrected rate of eighty per cent? What single or several factors might help us to improve this?

Dr. Drake: I think that the greatest single factor brought out by the panel today is that we should employ the improved culture technique which was mentioned.

Dr. Green: I think that proper education of every patient who is a possible host to this infection is a very important point. Many rheumatic heart disease patients do not know about subacute bacterial endocarditis. The physician needs constant awareness of this disease since index of suspicion is very important in early diagnosis.

Dr. Quinn: My own feeling is that one must try to recognize and treat these cases promptly. We do not have to wait always for positive cultures or classical clinical signs. Any patient with valvular or congenital heart disease that has a fever for more than a week has to be seriously considered as having endocarditis. A patient with rheumatic heart disease, for example, who comes in with acute pyelitis should be considered as a posible endocarditis case until proved otherwise. We must have a high index of suspicion.

BILATERAL AGENESIS OF UPPER EXTREMITY

JOSEPH L. FLEMING, M.D.*

Every doctor is, to some extent, an expert in rehabilitation. The word simply means helping a person by many and various means to achieve maximum biological efficiency. No one group may rightfully lay exclusive claim to the word and, in fact, by its nature the rehabilitation process is necessarily a team project in which each specialty group plays its role under the coordination of the specialist in whose field the major disorder lies.

Optimism is the chief password in the rehabilitation process and many a forbidding sentinel of hopelessness will step aside when this magical word is invoked. In orthopaedic surgery we have found it a good rule when dealing with severe disruption of function, whether congenital, traumatic or infectious, to assume the best possible outcome and to treat vigorously on the assumption that some day the child may be able to walk. For example, if a child with severe meningomyelocoele does not ever walk, it should not be because the orthopaedic surgeon has allowed the development of deformities of knees, hips and feet that prevent bracing and ambulation.

Looking backward on the case of Patricia K., it seems obvious that she would walk, use artifical arms, feed herself and attend school, but if it were not for the optimism bred by the despair of her mother, she would still be in her cart, writing and eating with her feet, and deprived of the advantages of association with other children in school.

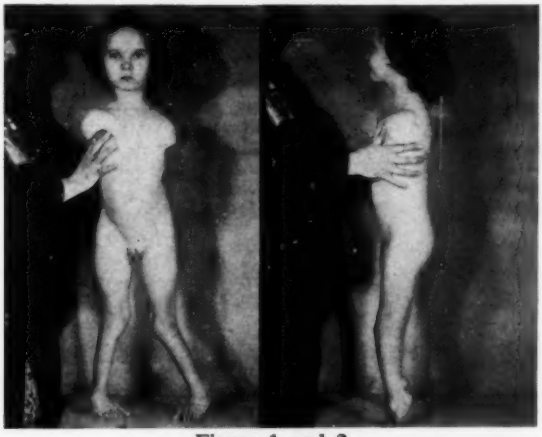

Figure 1 and 2

Standing with support before treatment.

Patricia K. was born in 1948 of normal parents and following a normal pregnancy. There was a complete agenesis of the arms although the scapulae and clavicles were normal. There were bilateral clubfeet, bilateral absence of the fibulae, and bilateral congenital dislocation of the hips. There was a moderate right dorsal scoliosis.

The hips were reduced by Dr. Gehring of Detroit and the feet were casted for a year until the parents discontinued treatment. At age 3, an attempt at bracing and

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ambulation failed, at least partially due to the severe foot deformities.

When first seen in 1953 she was four and a half years old. She was transported by her mother in a cart and it was becoming increasingly difficult for her mother to lift her. The chief reason for the parents bringing the child was to see if a way could be found for the child to walk or to gain some increased independence.

Patricia could be stood up but required a good deal of help from supporting hands. The arms were absent and in the glenoid fossa was a slightly protruding pad of thick fat. The musculature of the shoulder girdle was relatively good except for weak pectorals. There was a moderate right dorsal scoliosis of 27 degrees. Both hips were stable although x-ray revealed that the right hip was dysplastic and subluxated. Both knees were very unstable and dislocated anteriorly on extension. The fibulae were absent.

The feet had grossly defective musculature especially the anterior tibials and peroneals. There were semi-rigid equinovarus deformities of severe degree.

Figure 3

Figure 4

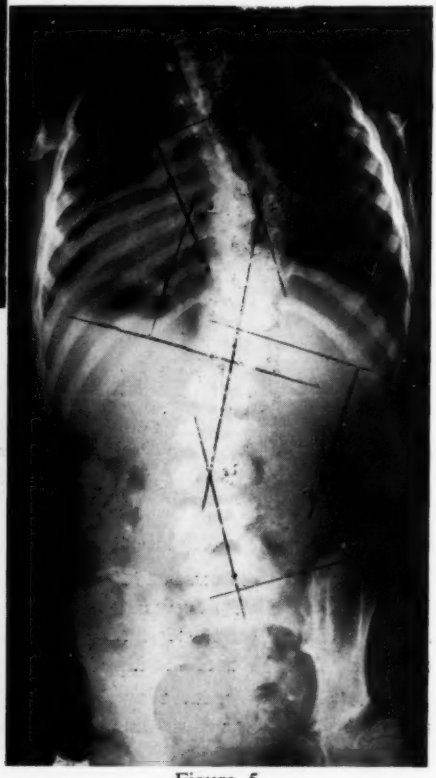

Figure 5

Figures 3, 4 and 5 — Congenital scoliosis and equinovarus foot deformities.

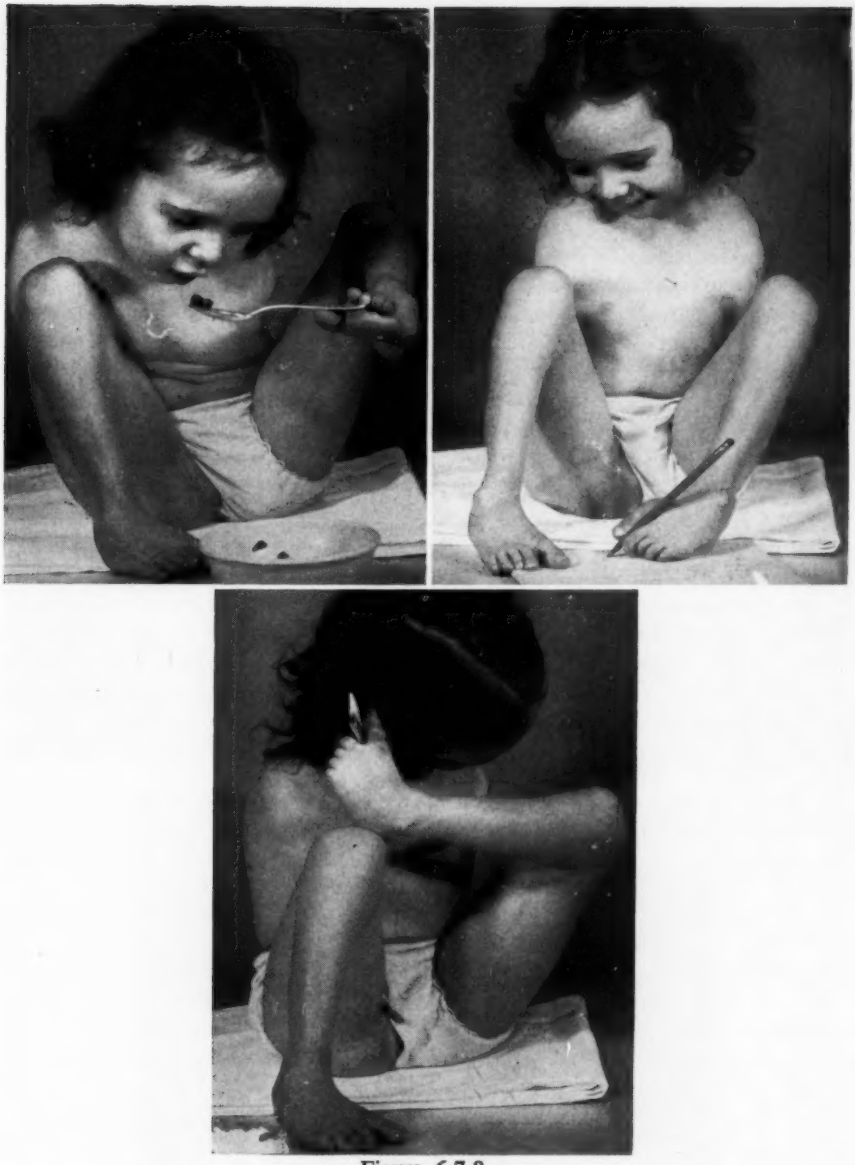

Figure 6-7-8

Skill in use of feet, age 4 years.

In spite of these deficiencies, she had developed an astounding skill with her feet. She was able to feed herself, write, color, comb her hair, etc. The hallux functioned much as does a thumb. Sitting down, with her shoes off, she had remarkable efficiency. She pushed herself about the floor very efficiently. All in all, an attractive and

charming sight in a four-year old but not so acceptable in a woman of fifty.

Psychological testing disclosed an I.Q. of 85 which was considered a minimal score.

Patricia was seen in consultation by many physicians from many specialities and opinion was unanimous and vociferous that nothing should be done to the child in order to make her walk that might endanger the use of her feet as hands. In addition, it appeared to everyone after seeing her that due to the multiple defects and deformities that independent walking was most unlikely, and the great fear that we would lose her abilities without gaining anything.

The parents however strongly supported the orthopaedic view that to walk, to attend school, was at least as important as the possible partial loss of prehensile pedism. The mother's words, "I can always feed her and comb her hair but I can't always lift and carry her," precipitated the decision to proceed with her rehabilitation.

First the feet were wedged with plaster casts, out of forefoot adduction. This required six weeks and was stopped short of full correction because of the fear of developing severe deformities which are usually present when the fibulae are absent. The feet then could be brought passively to the neutral position from their previous position of thirty degrees of forefoot adduction.

Next the feet were wedged out of the position of thirty degrees of equinus. This proceded very slowly and consumed ten weeks. The feet could now be brought up to the neutral weight-bearing position. They were very stiff and loss of function was feared. The corrected position was maintained by passive stretching, night casts and active exercises while the Physiotheraphy Department worked on developing the upright muscles — the quadriceps femoris, gluteus maximus and spine extensors — all of which had been of very poor quality due to disuse. A fracture of the tibia further prolonged this stage. After four months of intensive physiotheraphy and a strenuous home exercise program, she was able to walk with help but by herself she could balance only for a few seconds. She had regained full use of her feet.

A Taylor spinal brace was fitted with a short length of broom stick attached by a swivel joint to its back. With this apparatus the parents could walk her about for long periods, gradually decreasing the amount of assistive balancing. She was taught

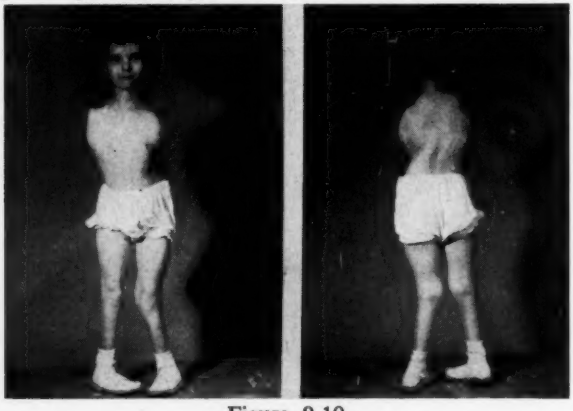

Figure 9-10
Standing alone after treatment.

to use her head to replace the normal balancing function of the arms. After four weeks with the brace, ten months after her treatment began, she walked independently. The stability of the knees increased as the quadriceps were developed and tibial osteotomies, previously considered, were not indicated. She was trained to rise from a sitting position and also taught how to fall without injury.

About this time an Amputation Clinic was developing at this hospital under the direction of Dr. C. Leslie Mitchell, and previously unfittable upper extremity amputations was now being prescribed for. Patricia was trained in the use of a right shoulder disarticulation prosthesis and within a few weeks had mastered the fundamentals. Six months later a left prosthesis was prescribed and she has become proficient in its use as well. These prostheses are controlled by contralateral shoulder harnessing and ipsilateral thigh harnessing.

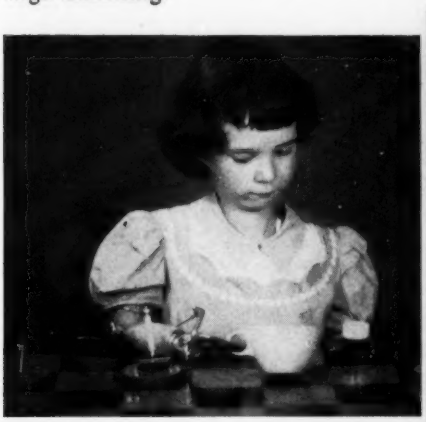

Figure 11, 12, 13, 14 — Skillful accomplishments, age 9 years.

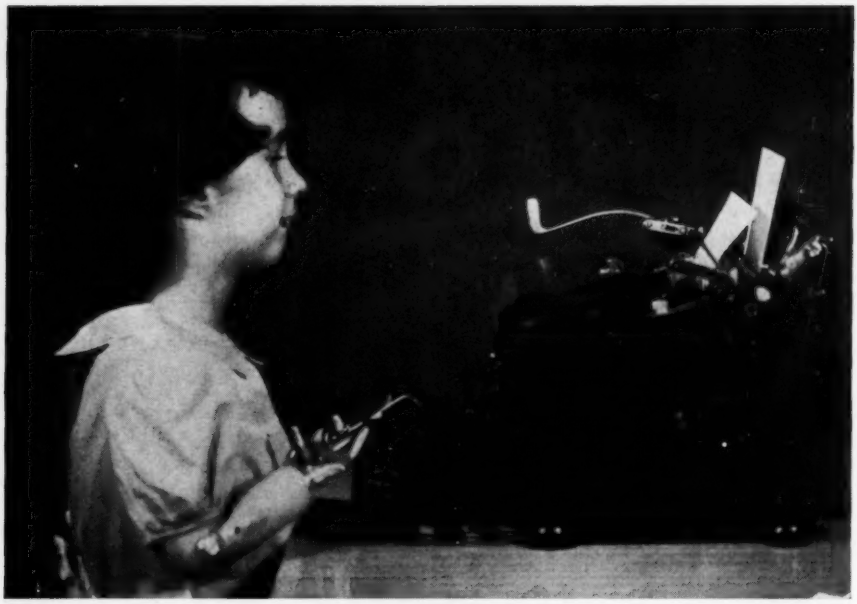

Figure 11-12-13-14

Skillful accomplishments, age 9 years.

A partial list of her accomplishments are: 1. Feeds herself pre-cut food with adapted utensils. 2. Brushes teeth, washes face, combs hair. 3. Types with two hands. 4. She attends school and camp for handicapped children. 5. She is fully independent in school except for dressing and personal hygiene. 6. She is now included in children's activities at home. 7. She keeps her shoes on all day and is using her feet only occasionally and in private.

Many problems still lie ahead for this child. It is possible that the hips and knees and feet will deteriorate with use and so diminish her efficiency in walking. However, this would be equally true for her efficiency in using the feet as hands. She will need long continued and expensive care in the future with regard to her prostheses. She is now potentially employable and her increased independence has been gratifying to all.

This child was cared for under the Michigan Crippled Children's Commission program with the invaluable co-operation of Dr. Clarence Eisman, M.D. She was fitted with her prostheses by Dr. James Glessner, M.D. and Dr. Charles Long II, M.D. and was trained in their use by Miss Powell of Occupational Therapy. Mr. Tony Fillipis of Wright-Fillipis was the prosthetist.

ISOTOPES IN MEDICINE

INTRODUCTION*

HOWARD P. DOUB, M.D.**

The electrifying news of the explosion of the first atomic bomb in Japan shocked the world, to which the term "splitting the atom" had previously indicated only a remote possibility. Sixty years earlier the world of physics was similarly astounded by Roentgen's discovery of x-rays, which was followed by Becquerel's recognition of natural radioactivity and the isolation of radium by the Curies. The modern production of artificial radioactive materials is a lineal descendant of these earlier discoveries.

The medical application of radioactive isotopes follows three main lines; (1) diagnosis, (2) therapy, and (3) research, physiologic and biologic. In this brief review we will direct attention to some of the more significant uses to which isotopes have been put. No attempt will be made to cover the entire subject or to deal with it in detail.

Radioactive iodine (I^{131}) has been of great value as a biologic tracer, since the thyroid concentrates iodine selectively. The isotope has a half-life of 8 days and emits both beta and gamma rays, permitting study of its concentration by surface measurements. This makes possible accurate studies of thyroid function in benign and malignant states. In cases of thyroid carcinoma whose metastases concentrate I^{131}, a potential therapeutic effect enters into consideration, although the possibility of damage to the hematopoietic system and other structures leave this question to be decided by future research.

Radioactive phosphorus (P^{32}) has a half-life of 14.3 days and emits beta radiation. Its high concentration in bone and bone marrow, liver, spleen, and lymph nodes, and in the nuclei of actively multiplying cells, has prompted its use in the detection of soft tissue and osseous metastases and in determinations of the activity of bone growth, especially in the epiphysis. The uptake of this isotope by both erythrocytes and leucocytes make it a therapeutic agent of value in certain blood dyscrasias.

Radioactive sodium (Na^{24}) has the disadvantage of a short half-life of 15 hours — which makes it difficult to obtain and use, as it cannot be stored. It is valuable, however, in biologic and clinical studies. It has been used in the determination of extracellular fluid and of circulation time and to demonstrate impairment of peripheral circulation.

The therapeutic possibilities of radioisotopes are intriguing and have been widely investigated. I^{131}, because of its high uptake in cases of hyperthyroidism, has seemed to be particularly well suited to the treatment of that condition. A study of the various reports in the literature indicates a wide variety of opinion on the subject. There is no doubt of the effectiveness of this isotope in producing remissions of the disease. The difficulties lie in the standardization of dosage and the amount of study necessary in the pretherapeutic stage. Fear of a possible carcinogenic effect has deterred

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*This introduction and the following paper are the first of a series on isotopes in medicine to appear in the Bulletin.

**Consultant, Department of Radiology

some. The possibly adverse effect on the hematopoietic system has caused others to voice a word of caution. Administration of I^{131} has also been used to reduce thyroid function in order to lessen the work load on the heart.

Radioactive phosphorus, has been of considerable value, therapeutically, in controlling polycythemia vera and is widely used for this purpose. Leukemia has developed in some of these treated cases, but since it is known to develop also in the absence of such treatment P^{32} cannot be accepted without qualification as the cause. In some of the chronic leukemias P^{32} has been an adjunct in treatment. It has been found, however, to be of more value in chronic myelogenous leukemia than in the chronic lymphatic type. In some cases the enlarged spleen has not regressed satisfactorily. Acute leukemias have not reacted favorably to radioactive phosphorus; Hodgkin's disease has shown only slight improvement, but in lymphosarcoma evidence of regression has sometimes persisted for several months. Recently the combination of radioactive phosphorus and oreton have shown favorable results in the control of metastatic bone lesions from cancer of the breast.

Radioactive gold, which has a half-life of 2.7 days, has several interesting therapeutic applications. In cases of metastatic carcinoma of the abdominal and pleural cavities direct injections of colloidal radiogold has produced encouraging palliative results, in the form of marked decrease in fluid formation and clinical improvement. in cases of cervical carcinoma radiogold injected into the parametria has been shown to permeate along the lymphatics, with destructive effects. This may prove to be of future importance, Radiogold is also used as a research tool to follow lymphatic drainage routes. Seeds of this isotope do not require removal because of their short half-life.

Cobalt 60, which has a half-life of 5.3 years, has taken a prominent place in radiotherapy. The radiation thus produced is equivalent to 3-million-volt radiation and is useful in the treatment of deep-seated malignant tumors. Cobalt is also valuable in the form of needles and removable seeds.

Cesium^{137} is a waste fission product from nuclear reactors, and has a half-life of 37 years. The gamma radiation is about equal of that of one-million-volt radiation. This isotope may soon be generally available.

Strontium^{90} surface applicators have been found valuable in superficial lesions of the cornea and conjunctiva. A number of other isotopes have had limited usage, but space does not permit mention of the entire list. Intracavitary therapy with some sort of plastic bag containing various isotopes has been found useful in superficial mucosal lesions.

The discovery of artificially produced radioactive isotopes has produced a tremendous impact on the medical world and has provided tools for research along lines previously unthought of. The great hope for a constitutional cure of cancer has, however, not been realized. Discovery of substances which would remain localized in the tumor without delivering generalized radiation would greatly aid in this problem, but this is still an elusive dream. Cobalt 60 and cesium^{137} are excellent adjuncts to our therapeutic armamentarium for external irradiation, just as radiogold and radioiodine are valuable for internal irradiation. The first chapter of this fascinating subject has been written in the past decade. The results of clinical and research work in the coming decades will determine the contents of succeeding chapters.

EXPERIENCE WITH INTRA-CAVITARY RADIOGOLD AT HENRY FORD HOSPITAL

M. J. BRENNAN, M.D.*
K. D. MCGINNIS, M.D.**
L. PREUSS, M.S.***

Radiogold was introduced into therapy for effusion at Henry Ford Hospital in March, 1952. Since that time 42 patients have received injections of colloidal gold (Au^{198}) into serosal cavities for the palliation of serosal effusions secondary to malignant processes. Au^{198} has been used because of its suitable half-life of 2.7 days and its radiation characteristics. This isotope emits a beta particle with an average energy of 0.97 MEV and a gamma component of 0.41 MEV. The beta emission has a mean path in tissue of 3.8 mm and is responsible for therapeutic effect. The gamma emission is responsible for the chief health hazards involved in the clinical use of Au^{198}.

Methods and Dosage: Methods for safe-handling of radiogold have been described elsewhere[1,2]. Exposure for the physician during the process of administration usually does not exceed 20 milliroentgens by direct measurement. This level is well within the maximum permissible daily exposure of 50 milliroentgens. The patients have been kept in private rooms until the residual radio-activity was less than 30 millicuries of gold; individually calculated time-distance precautions are provided for the protection of medical and nursing personnel, and visitors, during the post-administration period.

Single doses ranged from 75 to 150 millicuries in the twenty patients who were given intraperitoneal gold and who lived more than one month following the instillation of gold. There was no correlation of length or frequency of good effect with dose in the intraperitoneal group. (Table I) The present series is not large enough to establish optimal dose levels. However, Kniseley[3] failed to find pathological evidence of acute radiation complication in patients given gold in quantities as large as 659 millicuries intraperitoneally in ten months. Five of the seven patients given 150 millicuries intra-abdominally in this series had good results, while three of five given 75 millicuries had good results. In view of the lack of knowledge concerning mechanism of action of radiogold and the desire of insuring adequate dosage, the large amounts have been preferred inasmuch as no radiation complication occurred in this entire series of 42 treatments.

Results:

Only patients who survived more than three months under observation have been considered in the calculation of determinate results.

ASCITES GROUP

Determinate Good Results:

Determinate good results are restricted to those patients who, having previously required paracentesis, experienced control of their effusion for more than three months following gold instillation. By control is meant freedom from the necessity for para-

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centesis for a minimum period of three months. Six of the definitive good results noted in Table I remained free of ascites from six to thirteen months. Four cases required paracentesis again at three and one-half, four, five and six months respectively.

TABLE I

ASCITES GROUP OF THIRTY PATIENTS. SINGLE INTRAPERITONEAL INJECTION OF RADIOACTIVE GOLD WITH RESULT

	150 mc.	125 mc.	100 mc.	75 mc.	50 mc.
Definitive Good Results (10)	Ovary Ovary Mesothelioma Schwannoma Breast	Ovary	Ovary	Ovary Adenoma Ca. Endometrial Ca.	
	150 mc.	125 mc.	100 mc.	75 mc.	50 mc.
Probable Good Results (1)	Ovary				
	150 mc.	125 mc.	100 mc.	75 mc.	50 mc.
Prophylactic (6)	Ovary Ovary Ovary Ovary	Ovary		Adeno Ca. Stomach	
	150 mc.	125 mc.	100 mc.	75 mc.	50 mc.
Failures (4)		Ovary	Ovary	Ovary Colon	
	150 mc.	125 mc.	100 mc.	75 mc.	50 mc.
Indeterminate (9) (6 dead)	Ovary Renal		Ovary Ovary Ovary Ovary Pancreas	Fibrosarcoma	Ovary

Probable Good Results:

Probable good results are tabulated for a group of patients observed from a minimum of five to a maximum of twelve weeks after therapy. One such patient is apparently well controlled seven weeks following the administration of radiogold and no longer has demonstrable peritoneal effusion.

Prophylactic Group:

Six patients without ascites were given intraperitoneal gold prophylactically when surgery disclosed ovarian carcinoma already involving the peritoneum in five, and carcinoma of the stomach metastatic to the ovary in one. Of these patients three

remain free of ascites five, six and fifteen months after gold treatment. Two patients died after two and six months, respectively, of progression of intra-abdominal disease demonstrated at autopsy. Nevertheless, they remained free of ascites until death. In a sixth case death occurred six months after gold treatment, but paracentesis was not needed until one week before demise.

Failures:

Definitive failures are those in which adequate time for development of therapeutic benefit has elasped and in whom paracentesis has continued to be necessary at intervals of three weeks or less following radioactive gold treatment. Four such patients were seen.

Indeterminate:

Cases are designated as indeterminate when death or loss from follow-up occurred within one month of the time of administration of gold. This time is considered too short for the success or failure of treatment to become apparent. Seven patients who died within this time interval and three whose records are incomplete are included in this category.

PLEURAL EFFUSIONS

The intrathoracic group has been divided into categories constructed on the same criteria as those explained above for the ascites group. Results in these patients are seen in Table II. Dosages in this group ranged from 50 to 75 mc.

TABLE II

PLEURAL EFFUSION GROUP OF TWELVE PATIENTS. SINGLE INTRAPLEURAL INJECTION OF RADIOACTIVE GOLD WITH RESULT

Millicuries Radiogold	75 mc.	50 mc.
Definitive Good Results (3)	Breast	Breast Mesothelioma
	75 mc.	50 mc.
Probable Good Results (1)	Breast	
	75 mc.	50 mc.
Failures (1)	Breast	
	75 mc.	50 mc.
Indeterminate (7)	Breast Breast Colon Thyroid Adeno Ca. Cervix	Breast

COMPLICATIONS

One patient developed generalized coliform peritonitis immediately after paracentesis for gold therapy and died four days later. This patient was autopsied, but evidence of bowel perforation was lacking and the gold was found evenly distributed throughout the peritoneal cavity without intensive local effects at any point. The possibility that gold interfered with the patient's defense against peritonitis, attributable most probably to the paracentesis itself, cannot be excluded. Although Botsford[4] has recorded bone marrow hypoplasia with areas of focal necrosis following intracavitary radiogold, in no instance in this series was leukopenia seen and the patients remained free of thrombocytopenia and hemorrhagic manifestations. In those patients who were followed for a long period of time no evidence of late radiation anemia developed.

DISCUSSION

Examination of recorded clinical data undertaken for the purpose of finding information of prognostic value with regard to the probable usefulness of radiogold in the treatment of ascites shows that the most responsive group of patients are those who present with relatively early disease as manifested by a lack of hepatomegaly, absence of palpable abdominal masses and absence of blood in the serosal aspirate. Experience here substantiates the findings of others with respect to the usefulness of this mode of therapy[5,6,7,8] in the management of ascites due to malignant disease.

The efficacy of radiogold in controlling effusion due to metastatic malignancy is not derived from actual control of the disease process itself as is revealed in two of the prophylactic cases who, in spite of progression of intra-abdominal disease, continued to have control of ascites. While Goldie and Hahn[10] observed destruction of sarcoma 37 cells intraperitoneally in the CFW mouse following intraperitoneal gold, Stembridge has shown that carcinoma cells persist in apparently viable state after gold infusion even though ascites does not recur.[11] Autopsy studies have demonstrated extensive superficial fibrotic change in tumor and in the serosa itself in patients treated with radiogold.[3] There is no evidence of effect on malignant cells lying more than 2 or 3 mm. below the surface.[9]

Therefore, when sterilization of serosal metastases is being attempted, intracavitary gold may be thought of as a supplement, but certainly not a substitute, for external irradiation.

The tolerance of patients for abdominal irradiation given in close temporal proximity to radiogold treatment has not been determined. Therefore, one would hesitate to give intraperitoneal gold if it is thought that definitive radiation treatment rather than simple palliation is feasible.

SUMMARY

1. Intracavitary radiogold has proved useful for the palliation of malignant ascites and hydrothorax.
2. No complications attributable to radiation were seen in this series.
3. Effusion due to very far advanced malignancy, particularly in the presence of

hepatomegaly, palpable tumor masses and grossly blood fluid is seldom controlled by radiogold infusion.

4. Prophylactic use of radiogold appears to have been successful in delaying the complication of ascites in ovarian malignancy.

The authors wish to express their appreciation to Dr. A. Veldhuis for permission to use cases treated in the Gynecological Section in this study.

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ACUTE MILIARY DISEASE OF THE LUNG
DIAGNOSIS AND TREATMENT

M. A. BLANKENHORN, M.D.*

More than 80 conditions have been recorded where disseminated miliary lesions are seen in x-ray examination of the lungs. When such lesions are the sole objective evidence of morbidity differential diagnosis is difficult and any contributing information is welcome.

Dr. Benjamin Felson at the Cincinnati General Hospital has emphasized the help that comes from the observed rate of change, i.e. progression or regression and has arbitrarily set two weeks or less as the period of change in acute diseases—two to eight weeks as subacute—and failure to change after eight weeks as a chronic disease. This is a technique available to less experienced observers and is appreciated by those not specialists in radiology.

Infection due to bacteria, viruses, rickettsia, fungi, protozoa, and inhalation of specific irritants may all cause similar lesions. Such lesions occur also in disorders of unknown etiology such as primary atypical pneumonia or infectious mononucleosis. No inclusive report is attempted here, but typical examples are shown with reference to the rate of change using Felson's standards. It is impossible to show reproductions of the numerous x-ray films demonstrated in the original presentation. In abstract it can be accepted that these films are all much alike—in fact, they were chosen because they could not be distinguished from miliary tuberculosis. Therefore, the rate of change and certain laboratory tests are useful.

Miliary tuberculosis is the most common and perhaps the most important because of the need of early and energetic treatment.

Tuberculosis may make rapid progression and regression under treatment. It is seldom chronic as miliary only.

Felson's experience in 1952 was that one-half of the cases showed other intrathoracic abnormalities due to tuberculosis.

Because pure miliary tuberculosis is perhaps the most important topic in my discourse, I will enlarge upon it later but first go on to some of the other miliary diseases.

Histoplasmosis is being recognized with increasing frequency and resembles tuberculosis in many respects—there is usually slow regression—much slower than tuberculosis. The pure miliary form is rare. The rate of progression depends in large part upon the degree of exposure, i.e. the number of organisms inhaled.

Newer techniques for histopathology show histoplasmosis and tuberculosis to be simultaneous and co-existant in lung lesions.

There is little morbidity from histoplasmosis of the lungs only in adults except in epidemics where severe exposure has occurred in dusty employment.

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The material in this paper is an abstract of a presentation before the Henry Ford Hospital Medical Society, February 14, 1956, Detroit, Michigan.

Diagnostic measures, histoplasmosis:

1. Histoplasmin skin tests.
2. Complement fixation tests for histoplasmosis. Said to indicate active infection if positive.
3. Bone marrow culture.
4. Culture of abnormal fluids, if present.
5. Sputum and/or gastric cultures if pulmonary involvement is present.
6. Biopsy of accessible lymph nodes or of scalene fat pad. Specific diagnosis may be provided by demonstration of organisms in sections.

The prognosis is good except in those forms in which the blood stream is invaded.

Disseminated miliary lesions are an uncommon form of primary atypical pneumonia and difficult to prove, but they do occur.

Chicken pox and measles may show miliary lung lesions. There is rapid regression in measles but slow regression in chicken pox.

Bronchiolites fibrosa obliterans develops acute miliary disease usually due to the accidents of inhaling irritants. Examples are shown where no known irritant was discovered, but lesions found at autopsy were such. In non-fatal cases there is rapid regression.

Asthmatic miliary pneumonia has been seen 15 times at the Cincinnati General Hospital and published by Felson and Felson[1] as acute diffuse pneumonia in chronic lung disease. Here acute miliary nodulation occurs in a patient who usually has had asthma for a long time. During the attack of pneumonia eosinophilia is absent. The miliary lesions regress rapidly.

A few examples of pneumoconiosis are shown where the lesions are of a disseminated miliary type but different from tuberculosis in many respects—principally in being static.

Blastomycosis is a typical fungus disease with miliary lesions.

I wish now to enlarge upon the diagnosis and treatment of miliary tuberculosis. Miliary tuberculosis, in the experience of the Department of Medicine at the Cincinnati General Hospital, is essentially a problem in internal medicine. This accounts for the emphasis I put upon it and explains why I insinuate tuberculosis into a program for internists. Few doctors, except tuberculosis experts, have been interested until the recent era of chemotherapy. Early diagnosis and energetic treatment depends upon the the doctor who first sees the patient. We have had a generous experience at the Cincinnati General Hospital. What was formerly a rapidly fatal disease is now treated with remarkable success. Dr. J. Park Biehl, Assistant Professor of Medicine, has given me reports and treatment schedules for miliary tuberculosis which have not yet been published. From now on I am quoting Dr. Biehl. I concur in his emphasis upon the importance of lumbar punctures.

Routine of the Cincinnati General Hospital Department of Internal Medicine.

Diagnostic measures, miliary tuberculosis:

1. Tuberculin testing.
2. Lumbar puncture (to detect presence of meningitis). Culture of CSF x 2 for AFB if abnormality present.

3. Sputum examinations and/or 3 gastrics for culture and guinea pig.

4. Three 24 hour urine collections for AFB culture.

5. Biopsy of any tissue likely to show caseation (L-nodes, endometrium). Biopsy for miliary granulomata (e.g., liver biopsy) less satisfactory since granulomata thus found are not necessarily tuberculous. One frequently may surmise a granulomatous infection from the x-rays alone. Culture of bone marrow has been disappointing. No CSF culture has been positive in the absence of meningitis.

Treatment schedule, miliary tuberculosis:

1. Bed rest in hospital 3 - 6 months, according to home situation, then up and about at home for 3 more. Ability to return to work governed by the situation, mainly. Some have returned to light work 4 - 6 months after starting therapy.

2. Streptomycin ½ gm. plus dihydrostreptomycin ½ gm. q.d. for 2 months, then streptomycin 1 gm. twice weekly for a total of 1 year.

3. Isoniazid 20 mg./kg. daily in divided doses, with 300 mg. of pyridoxine daily, both for 2 months; then isoniazid 300 mg. daily alone for a total of 1 year. Pyridoxine is given to prevent peripheral neuritis seen when large doses of isoniazid are given. (Biehl and Vilter)[2].

4. Tuberculous isolation for 1 month, or until sputa are negative 2 months.

These factors stand out in the study of 56 *cases of miliary tuberculosis in adults observed from* 1951 *to the present.*

1. Age incidence: over 40% of the group were 60 or over.

2. Most of the younger women were or had recently been pregnant.

3. High preponderance of negroes (49/56). This is in keeping with our experience in extrapulmonary tuberculosis generally.

4. Nonspecific nature of symptoms — those of infection in general; cough, weight loss, weakness, feverishness, anorexia, night sweats, dyspnea, chills and vomiting (chills in 13/51 who give any history). Headache and delirium pointed to meningitis. Duration of present illness was prolonged in some; 12/56 were sick for 10 weeks or more.

5. Paucity of physical examination: rales, fever. No splenomegaly.

6. Only 4 had had known tuberculosis previously. Except for 18 with meningitis, 25 (45%) had another form of tuberculosis present concurrently. This was recognized clinically in only 18 (pulmonary, pleural, lymph node, genito-urinary, bone, peritoneal involvement). Thus in 68% there was no clinical evidence of other tuberculosis.

7. Except when terminal with meningitis, leukocytosis was rare.

8. Diagnosis established by:

(a) demonstration of tuberculosis.

(b) demonstration of a grossly caseating granuloma.

Excluding 6, in whom the diagnosis was never suspected (usually terminal on admission), the diagnosis was made according to the above criteria in 44 of 50 patients. This was best achieved by sputum or gastric cultures, urine cultures, culture of serosal exudates, and biopsy of anything likely to reveal caseation, like nodes or endometrium. CSF was positive in 13 of 16 with meningitis. Tuberculins were negative in 7 of 20. Five of these were terminal cases and died.

9. Treatment: Start tuberculosis treatment in patients with subacute febrile illness, especially in negroes in whom x-ray shows miliary densities and for which no other

good explanation exists. It is not reasonable or necessary to await definite proof before starting therapy. Specimens should be obtained for this, of course, before or during first few days of treatment.

Response to therapy:

Fever: normal in from 2 days to 10 weeks — average 5 weeks.

X-ray change: Significant improvement has been noted within 2 weeks in 5, and lesions have cleared completely in 2 after 17 and 19 days treatment. Usually improvement seen after 4 weeks; most cleared by 16 weeks.

Bad prognosis:

1. Meningitis present — 6/18 lived.
2. Pulmonary tuberculosis — 0/8 lived.
3. Tuberculin anergy — 2/7 lived.

Relapse rate:

2 cases: one with subsequent miliary again, another lapsed treatment after 8 months and died of meningitis.

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AIDS IN DIFFERENTIAL DIAGNOSIS OF THE COMMONER TYPES OF ACUTE MILIARY DISEASES

(Adapted, 1955 from Felson, B.)[3]

Disease	*Laboratory Aids*	*Roentgenologic Aids*
1. Miliary tuberculosis	Lumbar puncture; biopsy; cultures	Progression
2. Histoplasmosis	Cultures; serological tests; skin test	Very slow regression; lymphadenopathy
3. Blastomycosis	Cultures; serological tests; skin test	Usually progression
4. Coccidioidomycosis	Cultures; serological tests; skin test	Slow retgression; lymphadenopathy
5. Acute diffuse pneumonia in chronic lung disease	No eosinophilia	Rapid regression; hilar enlargement
6. Bronchiolites fibrosa obliterans		Usually rapid regression
7. Loeffler's syndrome	Eosinophilia	Rapid regression
8. Primary atypical pneumonia	Cold agglutination	Rapid regression
9. Infectious mononucleosis	Blood smear; heterophile agglutination	Rapid regression; lymphadenopathy

CENTRAL RETINAL VEIN OCCLUSION TREATED WITH ANTICOAGULANT AND STEROID THERAPY: CASE REPORT AND DISCUSSION

DAVID BARSKY, M.D.*

Central retinal vein occlusion was noted by clinicians in the very early days of ophthalmoscopy. Michel[1], in 1878, was the first to publish the classical description; he concluded that most cases were due to thrombosis. Vehhoeff[2] (1906) contended that the occlusion was due to an endothelial proliferation. Since then there have been many controversies regarding the etiology of the occlusion. The general prognosis in untreated cases is poor and visual acuity usually decreases; 10% to 20% go on to hemorrhagic glaucoma and eventually enucleation. In keeping with the thrombosis theory, anticoagulant therapy has recently become a popular mode of management. However, the statistics are scanty and difficult to evaluate because many of the treated cases are of a selected group, and there is great variability with spontaneous recovery in many cases. Duff, Falls and Linman,[3] in 1951, reported that of a control (untreated) group of 70 patients with complete central vein occlusion, only 15% recovered above the level recorded at the initial visual acuity examination. Whereas, in 22 "selected cases" on Bishydroxycoumarin, 30% showed improvement of 0.1 or better over their initial visual acuity examination. The anticoagulant therapy was begun from 1 day to 5 weeks after the onset of symptoms and maintained for an average of 3 months. The prothrombin time was kept at 20% to 30% of normal. Gasparri,[4] in Italy (1952), reported "good" results in 64% of 25 cases treated with Tromexan anticoagulant. Klien[5] advocates a prolonged maintenance dose of anticoagulant in the preventive management of venous occlusion, by keeping the prothrombin time at about 50% of normal.

CASE REPORT

This 36 year old female was first seen at H. F. H. on March 24, 1955 with the complaint of blurring of the vision of her left eye for four days. The blurring had come on suddenly with no pain or redness. She had been seen three days previously by an ophthalmologist, who had diagnosed occlusion of the central retinal vein and referred her to the H. F. H. for treatment. She believed the blurred vision had come on almost instantaneously with no warning symptoms. The onset was not related to any trauma or associated general illness. Her corrected vision previously had been good in both eyes.

Past history revealed the patient had had nephritis at the age of 4 years, and scarlet fever at the age of 11 years. Following the latter, she had had attacks of arthritis and nephritis for a 4 month period, but no apparent sequelae after that time. Between the ages of 26 and 30 she had had 6 miscarriages, but with hormone therapy she had delivered 2 living children. Family history revealed one sister had healed tuberculosis.

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Examination on 3-24-55 revealed the following:

Visual acuity:	sc	RE: 20/70, LE: 20/80	
	cPC	RE: — 1.50 sph. + .50 cyl. x 150	= 20/20
		RE: — 1.00 sph.	= 20/40
Manifest:		RE: — 2.00 sph. + .25 cyl. x 130	= 20/20
		LE: — 1.50 sph. + .25 cyl. x 90	= 20/30

On external examination the position, lids, EOM, tactile tension, lacrimal apparatus, cornea, conjunctiva, sclera, anterior chambers and irides were normal. The pupils were central, equal and reactive to light and accommodation.

On slit lamp examination, both anterior segments were normal; and with the Hruby lens the right vitreous was normal, but some red cells could be seen in the posterior part of the left vitreous. Intraocular tension measured RE 17, LE 17 (Schiotz). Muscle examination revealed an NPC of 60 mms., and for distance vision and near vision there was vertical and horizontal orthophoria. Ductions were full and versions were normal.

Ophthalmoscopic examination showed the following: RE; Media clear. Disc normal in size, shape and color, with physiological cupping of normal depth. The retinal vessels were normal. On the superior nasal border of the disc there was a juxtapapillary area of chorioretinal atrophy approximately 2 disc diameters in size, with a margin of heavy pigmentation. The peripheral retina was normal. LE; Media clear. Disc margins blurred and difficult to make out. Retinal veins greatly dilated and tortuous everywhere. Throughout the retina, both peripherally and centrally and including all four quadrants, there was an extensive mottling of small scattered hemorrhages, with slight edema but very little exudate. In the macular area there was some slight edema with many small hemorrhages. In the inferotemporal quadrant there was an area of chorioretinal atrophy approximately 2 disc diameters in size, with a margin of pigmentation. In the center of this atrophic scar a retinal vein anastomosed with the choroidal circulation.

Initial impression was: 1) Occlusion of central retinal vein, left eye, 2) Old healed chorioretinitis, OU, and 3) Compound myopic astigmatism, OU.

The patient was admitted for immediate therapy with anticoagulants. In an attempt to minimize the reaction in the macular area, ACTH was started ten days after admission, being administered in the form of Armour's gel in a dosage of 30 u. twice daily. Vision in the left eye promptly improved from 20/40 to 20/25—. It was quite difficult to control the exact dosage of hedulin while the patient was on ACTH therapy and there was a great deal of fluctuation in her prothrombin time. The ACTH was discontinued after one week of therapy; however, on cessation of the ACTH vision in the left eye fell again to 20/70. The reaction in the left eye appeared to have settled and two days later the patient was discharged in the care of her local ophthalmologist, on a maintenance dose of hedulin 100 mgs. daily.

Eight days later he advised her to return to the Henry Ford Hospital for further therapy because examination by him at that time suggeted there might be an extension

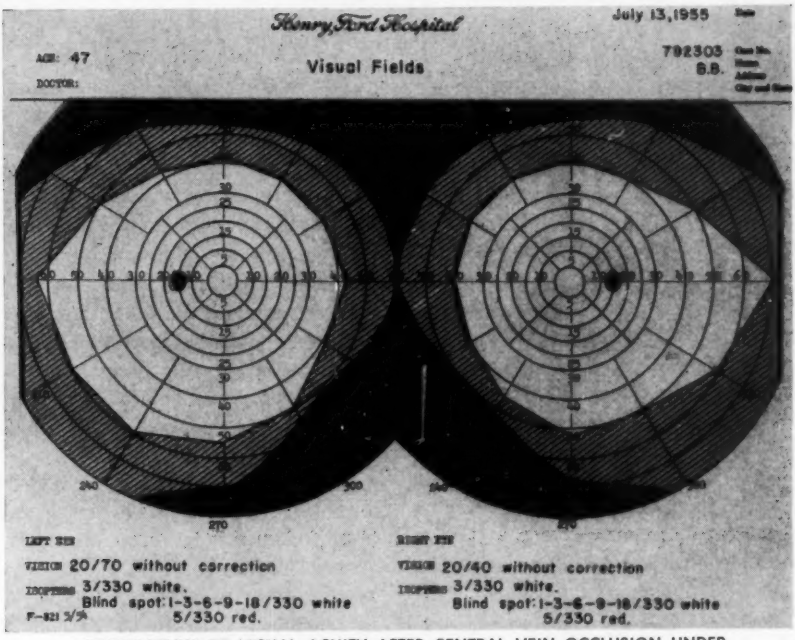
of the thrombotic process. Consequently the patient was readmitted on 4-22-55 and on this admission was found to have corrected visual acuities of RE 20/20 and LE 20/70. Tension was normal, OU. Ophthalmoscopic examination of the left eye showed no change except that there seemed to be a few more hemorrhages than had been noted at the time of her discharge. The patient was again placed on ACTH therapy 40 u. b.i.d. with a low salt diet and a supplement of 1 gm. KC1 daily. As the prothrombin time on the day of admission was found to be prolonged beyond the upper limit of 2 minutes, vitamin K_1 oxide was given intravenously. By the third day the prothrombin time had dropped back to within normal limits and hedulin was resumed. Throughout this hospital stay, too, anticoagulant therapy was quite irregular in its effectiveness and the prothrombin time ranged from 80% to 20% of normal, even though the daily dose of hedulin was correlated with the prothrombin time. It was felt at the time that ACTH might well have been the contributing factor to this irregularity. The ACTH was kept up for one week and then the patient was transferred to a regime of prednisolone 5 mgs. q.i.d. The patient's course in the hospital was otherwise uneventful except for occasional pain in the left eye. At the time of discharge on 5-3-55 the vision with correction for the right eye was 20/20 and the left eye vision was 20/70. The fundus picture was essentially the same as on admission.

After her discharge, the patient was maintained on prednisolone 5 mgs. q.i.d. and hedulin 100 mgs. daily on an OPD basis by her ophthalmologist at home for approximately 2 weeks. She was kind enough to return 4 weeks later on June 1, 1955 to permit us to observe her progress. Corrected vision in left eye had improved to 20/30, tension was 17 mms. Schiotz and the ophthalmoscopic appearance of the fundus was essentially unchanged except that a few of the hemorrhages had apparently disappeared.

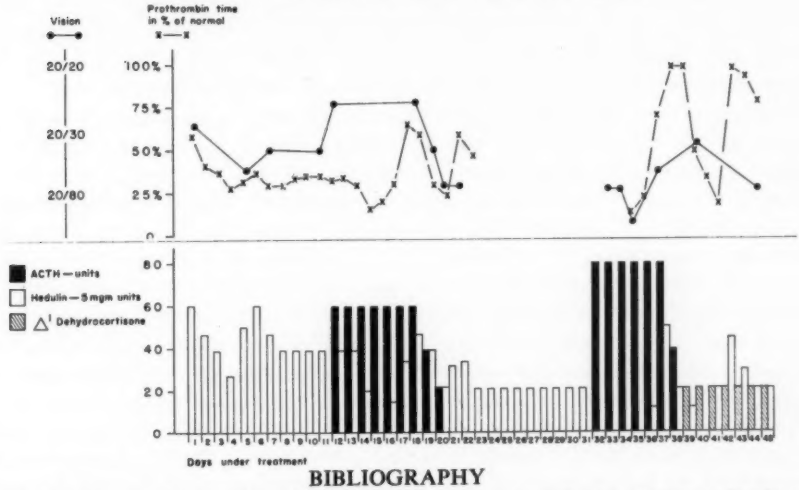
Perhaps the solution to the problem of evaluating anticoagulants in the management of venous occlusion lies in the recent suggestion of Maumenee[4]. He proposed that selected hospitals all over the United States be designated as treatment centers. On "odd days" of the year patients admitted with the diagnosis of venous occlusion would be placed on anticoagulants; on "even days" patients admitted could act as a control group and receive none. By standardizing the criteria for diagnosis of occlusion and the schema for the type and dosage of anticoagulants, a logical evaluation could be arrived at.

After evaluating anticoagulants, perhaps one step further, the value of steroids in the management of venous occlusion could be assessed.

Summary: A 36 year old white female was seen in the H. F. H. clinic with the diagnosis of central retinal vein occlusion, left eye, 4 days after the onset of symptoms. The patient was maintained on hedulin anticoagulant therapy for approximately 8 weeks with only irregular control of the prothrombin time. The irregularity was presumed to be in part due to the concomitant steroid therapy administered. Visual acuity on initial examination was LE: with correction 20/30; throughout the hospital stay the visual acuity tended to diminish but showed marked improvement when ACTH was added to the therapeutic regimen. On removal of the ACTH the vision again decreased. Visual acuity at final examination was LE 20/30 and the intraocular tension was normal.



CORRELATION OF VISUAL ACUITY AFTER CENTRAL VEIN OCCLUSION UNDER TREATMENT WITH ANTICOAGULANT AND STEROID THERAPY



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MYOFASCIAL PAIN SYNDROMES

Part III — Some Syndromes of the Trunk and Thigh

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In the two previous parts of this discussion, the syndromes presented could be most easily confused with neurologic disorders. However, in the trunk the differential diagnosis is most often between myofascial pain syndromes and visceral disease. In many cases it is found that visceral disease and a secondary pain syndrome exist concomitantly. Just as it is possible for a myofascial change to take place in the reference area of neural or skeletal pain, so is it possible in the reference area of visceral pain.

A difference exists in the mechanism of pain reference in neuroskeletal pain and visceral pain. The difference is one of transmission route only. The neuroskeletal pain most often travels somatic peripheral nerve fibers to the cord, while visceral pain most often travels autonomic nerve fibers to the cord. In both cases, mis-interpretation of the source of the pain (probably due to summation of cord impulses) is the common factor.

Once again it should be emphasized that myofascial pain syndromes, including the trunk group, may exist per primum and do not necessarily or usually signal underlying disease. In any case of pain in the chest or abdomen it is just as important to palpate the outside firmly as to auscultate the inside diligently.

THE ANTERIOR CHEST WALL SYNDROMES

The anterior chest wall syndromes have in common the occurrence of aching or sharp chest pain, often without radiation, sometimes brought on by activity, but not relieved by rest or food. Pain may awaken the patient at night; it may come on when the patient sleeps on the affected side, or may be unrelated to position. It is sometimes affected by weather changes, but is not accompanied by anything equivalent to the gelling phenomenon of the neck and shoulder group of syndromes.

The pain is usually not directly substernal, although in some cases it may be. The trigger area in such cases is felt by Travell to be in the rudimentary sternalis muscle[1], injection of which will relieve the substernal distress.

Pain in these syndromes usually occurs in one of four fairly circumscribed areas. In most cases the patient's pain directly overlies the trigger area. All of the myofascial pain syndromes of the chest seem to occur with more frequency on the left than the right.

The first area of involvement is in the upper half of the chest, usually overlying the converging fibers of the pectoralis major in the second and third costal or intercostal regions close to the mid-clavicular line. Tenderness may involve this entire section of the chest, or may be restricted to the size of a dime. Pain on occasions radiates to the shoulder or medial arm, and can exactly simulate anginal radiation.

This syndrome, the pectoralis major syndrome, may exist by itself[2], or in the presence of cardiac disease (usually coronary insufficiency). Relief of severe or recurrent pain by the treatment of the chest wall itself has been reported in acute myocardial infarction[3] and in pain following myocardial infarction[4].

The treatment of choice is injection of the offending trigger area. Oral steroids have been reported to be helpful[4], but this author has not used them widely. If the involved area is too broad to be easily injected, it may respond to local Ethyl Chloride

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spray. A word of caution — these injections may be painful and the sensitive anginal patient and his physician should be aware of the danger of precipitating angina during injection.

The second area of frequent anterior chest involvement appears usually in women and is located just beneath the breast in the midclavicular line in the sixth or seventh interspace or costal region. The pain is closely localized overlying the trigger area. It sometimes co-exists with a scapular trigger point and scapulocostal reference, thus being a secondary trigger within the reference area of the scapulocostal syndrome; another such secondary trigger is often along the same ribs in the mid-axilla.

This inframammary syndrome is usually seen on the left. It almost always responds rapidly to injection, and sometimes responds to the oral administration of antispasmodics or antacids. The latter clinical observation suggests the summation of gastrointestinal visceral impulses with chest wall somatic impulses. However, visceral involvement is not a sina qua non of this syndrome.

The third anterior chest wall syndrome, the costal margin syndrome, has its pain and its trigger point along the margins of the eighth, ninth and tenth ribs as they conjoin. I do not think it shows as much preference for left laterality as the two syndromes above mentioned. It responds rapidly to local injection.

The fourth syndrome is not strictly a "myofascial syndrome", but deserves mention as a soft tissue cause of local anterior chest pain. This is "Tietze's Syndrome", or the costochondral junction syndorme[5]. It is reportedly due to a chondritis or perichondritis of the costochondral junctions. It appears usually in the upper chest and responds rapidly to local infiltration of the costochondral junction, its surrounding intercostal spaces and its overlying musculature.

THE ANTERIOR ABDOMINAL WALL SYNDROMES

In the experience of this observer the most common locations of pain in the anterior abdominal wall syndromes are in the center of the lower quadrants and the superior margins of the upper quadrants of the abdomen. Here again the trigger area and the pain reference area overlie each other. The lower quadrant area is located close to McBurney's point, or in the corresponding location on the left. The upper quadrant areas are located along the costal margins at the conjoining of the cartilages of ribs eight, nine and ten in an area adjacent to that involved in the costal margin syndrome. The difference between these syndromes is more than a semantic one, since the abdominal syndrome seems to be mainly muscular in origin, while the costal margin syndrome seems largely connective tissue in origin.

The differential diagnosis of the abdominal wall syndrome includes the entire spectrum of gastrointestinal disease. Its pain is differentiated most characteristically by its continuity, its lack of relation to ingestion of food or to evacuation, and sometimes by its relation to motion. The patient can often describe the pain as being in the abdominal wall if he is specifically asked about the depth of the pain.

The abdominal wall syndromes can be easily differentiated from visceral pain syndromes by physical examination. The painful area is compressed rather firmly beneath a single finger or thumb, with sufficient pressure barely to pass the threshold of pain. The patient is then asked to raise both legs straight, causing both heels to leave the examining surface by a distance of a few inches only. The resultant contraction

of the abdominal wall will push the examining finger away from the viscera and simultaneously increasingly compress the abdominal wall beneath the finger. If, on this maneuver, the pain increases it is of abdominal wall origin; if it decreases it is of visceral origin.

Sometimes the muscular area will overlie the tender visceral area — as in an upper wall syndrome overlying a peptic ulcer.[6] In such cases the duality of pain etiology will also be apparent by using the above maneuver.

Treatment is by injection with an anesthetic agent and Hydrocortisone. The results of therapy will depend even more than in other syndromes on the accuracy of injection. The injection is made through all the layers of the abdominal wall in which the operator feels safe with his needle. An attempt is made to deposit the solution at each fascial layer and in each muscular layer of the involved portion of the abdomen. If tenderness has not disappeared after injection, the area should be re-entered and re-infiltrated.

THE PELVIC FLOOR SYNDROMES

The pelvic floor syndromes are among the most controversial of the myofascial pain syndromes. Thiele[7], one of the original collectors of cases of these syndromes, reports them as a common cause of coccygodynia. In addition to coccygodynia, myofascial affections of the pelvic floor may produce pain in the buttock, under the sacrum, in the lateral portions of the hip, or in the posterior thigh.

There are certain characteristics common to the pain of the pelvic floor syndromes regardless of the area to which the pain is referred. The most common complaint is an inability to sit comfortably on hard surfaces, or even on soft ones for prolonged periods. The patient must shift his position often and tries to keep his weight off the area of referred pain. Not only is it painful to remain sitting, but it is also painful to go through the motion of standing up or sitting down. Sudden twists of the pelvis or hips (as in changing direction during walking) may cause acute exacerbations of pain for days. Defecation may be painful, but this symptom is not a necessary criterion for diagnosis. These syndromes do not seem to be a cause of dyspareunia.

Trigger areas for the pelvic floor syndromes may be closely localized or may involve most of the pelvic floor. The muscles involved include the piriformis, the coccygeus and the levator ani. Involvement of the muscle can be identified not only by the soreness encountered on digital rectal examination, but also by a tight, fibrous, nodular feel of the involved muscle. I am not certain that differential radiation of pain from these several muscles can be predicted; however, in general the piriformis sends its pain directly under the sacrum to the coccyx, or down the back of the thigh, while the levator and coccygeus send their pain centrally to the coccyx or laterally to the buttock or hip. Primary involvement of the piriformis can often be identified by tenderness in the buttock externally over the greater sciatic notch.

Secondary neural involvement is reported to occur in the piriformis syndrome in a manner analogous to that of the scalenus anticus syndrome[8]. Involvement of the piriformis by a myofascitis may involve the contiguous sacral nerves (one, two and three) or the main trunk of the sciatic. Some cases of "sciatica" may thus be due to piriformis myofascitis.

Certain characteristics of these syndromes help differentiate them from primary neurologic lesions, such as herniated discs, cord tumors, and osteoarthritic nerve com-

pression syndromes. These characteristics include the early appearance of pain on straight leg raising, the common presence of a gelling phenomenon in the affected hip, and a close correlation of reproduction of pain on palpation of the affected muscles. Tense persons seem to have a predilection to the development of these disorders. In all cases except the secondary manifestations of the piriformis syndrome there are no changes in reflexes, motor or sensory findings, or bowel and bladder control.

Massage is the easiest method of treatment and is the treatment of choice in most cases. It is carried out in a manner similar to prostatic massage, with deep centripetal strokes repeated slowly for one or two minutes over the involved area. The patient is expected to have pain during the massage, usually with reference to the site of spontaneous pain. A course of four to eight massages (given once or twice weekly) usually suffices to produce a remission and often a cure.

Injection is the treatment of choice only in specific cases. These include (1) those refractory to massage, (2) those involving the piriformis too far laterally to be reached per rectum, and (3) those involving the levator or the coccygeus close to the coccyx, and having small trigger areas. The latter can be easily injected by the clinician using a bimanual method, palpating per rectum to check the position of the needle tip.

The upper reaches of the piriformis are unassailable by either injection or massage. Injection of the lateral reaches is carried out in this institution by the Anesthesiology Division.

THE ADDUCTOR LONGUS SYNDROME

This syndrome is worthy of mention mainly because of its confusion with osteoarthritis of the hip. The pain produced in the two diseases is quite similar and the differential diagnosis is made primarily by physical examination.

The pain of the adductor longus syndrome is located in the medial thigh near the groin, and/or along the medial stretches of the inguinal ligament and its proximity. Pain radiates usually along the medial or anterior thigh superficially to the knee. It is increased by weight-bearing or especially by sudden twists of the hip. It is often accompanied by a gelling phenomenon.

The pain of degenerative arthritis of the hip is usually deeper in the groin and is more likely to be referred laterally than medially. If it is referred to the knee it is more often deep in the knee.

The adductor longus trigger point is identified by tenderness at the origin of the adductor longus and in its upper three or four inches below the origin. This muscle is palpated easily as the major component of the adductor ridge along the medial, upper thigh.

The treatment of the adductor longus syndrome combines injection with decreased weight bearing. The patient must be given crutches or a carefully graded walking program. Continued weight bearing will defeat or prolong the injection program; one twist of the hip can set treatment back to the beginning.

Injection must be made deeply and carefully, beginning with the more tendinous portions of the muscle near its origin and infiltrating widely the belly of the muscle below the origin. This is one of the more gratifying myofascial pain syndromes to treat when isolated. However, it unfortunately often occurs as a secondary finding in the presence of osteoarthritis, compounding the difficulty of diagnosis and partially frustrating treatment. Treatment is nevertheless worthwhile even if there is underlying hip pathology.

SUMMARY

The myofascial pain syndromes constitute an interesting and often undiagnosed group of disease entities. Their recognition is dependent on common characteristics of symptoms, including aching pain, weather effect, tiring effect, and the gelling phenomenon. They usually respond favorably to a therapeutic program including local heat, salicylization, injection with hydrocortisone anesthetic solutions, ethyl chloride spray, massage, environmental manipulation, steroids, stretching, or the relief of tension—in the appropriate combination.*

*Since the publication of the first of this series six months ago, further experience has produced two modifications of therapy: (1) There is no apparent contraindication to direct mixing of Procaine Hydrochloride and Hydrocortisone Acetate. The mixture used in this clinic is 25 mgm (1 cc) of Hydrocortisone suspension in 9 cc of 1% Procaine Hydrochloride. (2) Increased therapeutic efficacy of salicylization may be produced by the concomitant administration of Flexin (Zoxazolamine)—250 to 500 mgm orally three or four times daily.[9] Flexin may be tried alone in the same dosage. Its efficacy in either case is not proven.

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NEUROLOGICAL DISORDERS ASSOCIATED WITH HEPATIC DISEASES*

RICHARD R. KNOWLES, M.D.**

INTRODUCTION

The recent application of biochemical methods to the investigation of neurological diseases holds forth the promise of clarifying the pathogenesis of many of the diseases of the central nervous system which previously had been non-specifically described as toxic or degenerative in nature. The most productive investigations in this sphere have been those performed on hepatolenticular degeneration and on hepatic coma. Below is presented a brief review of the results of these investigations and the current feelings regarding the biochemical defects and pathogenesis of these entities.

HEPATOLENTICULAR DEGENERATION

Wilson's disease is a familial disease with signs and symptoms secondary to pathological changes in the central nervous system (especially the basal ganglia), the liver and the cornea. Pathologically, the gross nervous system changes consist of varying degrees of atrophy of the cerebrum and the corpus striatum, especially the lenticular nuclei. These changes may be so severe that actual cavitation occurs in the basal ganglia and even in the cerebral cortex. Microscopically, there is a wide-spread loss of neurons with a diffuse increase in glial cells, especially the astrocytic series which undergoes a rather prominent hyperplasia. These changes are most pronounced in the cerebral cortex and in the basal ganglia, and are remarkably similar to those seen in manganese poisoning. The protoplasmic astrocytosis is identical to that seen in patients dying with hepatic coma. The liver shows the characteristic changes of the postnecrotic type of cirrhosis with many small nodules which vary considerably in size and are separated by wide fibrous tissue trabeculae. The cornea shows fine yellow granules in Descemet's membrane. The selective involvement of the basal ganglia is felt to be the result of the highly vascular nature of this area and hence its susceptibility to respiratory enzyme inhibitors. A similar selectivity is seen also in carbon monoxide, cyanide, manganese and carbon disulfide poisoning, all of which are well known inhibitors of respiratory enzymes.

Clinically the usual course is characterized by onset during adolescence, although it has been noted as early as the age of four and as late as the age of forty-five. The disease is slightly more common in males and there is much suggestive evidence that it is inherited as a recessive trait. Usually the signs of liver disease are not prominent, although in a few cases they have appeared early — even before neurological disease has become apparent. The liver function tests, however, and liver biopsy are always abnormal. The neurological picture is as varied as one might expect from the pathology, but basal ganglia signs are almost invariably the most prominent, although on rare occasions cerebellar and cortical symtoms—intellectual deterioration and loss of emotional control — are the most prominent. The tremor varies both in nature and degree; it may be intentional in type, a classic Parkinson tremor, or, more characteristically, the flapping tremor which is seen in impending hepatic coma. The tremor is most commonly maximum in the distal portions of the extremities and consists of rhythmic

*Presented at the Neurology Journal Club of the Henry Ford Hospital on February 13, 1956.
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flexion-extension movements.

PATHOGENESIS

The first clue as to the biochemical lesion in hepatolenticular degeneration came in 1930, when Horowitz demonstrated an increased copper concentration in the brain and liver of patients with this disease.[1] The next significant developments occurred some 18 years later when Denny-Brown found a persistent amino-aciduria and increased urinary copper in several patients with this disease.[2]

Elaboration of these studies of copper metabolism have yielded some highly interesting and relatively specific deviations from normal in patients who suffer from this disease. The normal serum copper level is a highly constant one, varying less than 5 per cent from the normal of approximately 110 micrograms per cent, while in patients with Wilson's disease the serum copper varies from 20 to 80 micrograms per cent. The normal urine contains from 0 to 25 micrograms of copper per day, while in patients with hepatolenticular degeneration the urinary copper content averages from 100 to 1,000 micrograms per day; that is, some 4 to 25 times more copper than normal. Various tissues have been analyzed for copper level and it has been found that the level in patients with this disease is ten times greater than normal in brain, liver and Descemet's membrane. Renal tissue also contains an increased copper concentration. Balance studies have shown that there is a definitely increased absorption of copper from the gastrointestinal tract in patients with Wilson's disease. The mechanisms controlling gastrointestinal absorption of copper have not been worked out, but it is probably dependent upon, and inversely proportional to the serum copper level. The serum transport of copper is felt to be highly, if not exclusively, dependent upon a specific plasma protein called ceruloplasmin. Ninety per cent of serum copper is bound to this protein. In Wilson's disease ceruloplasmin is at a low level.

In normal patients there is a relatively constant urinary output of small amounts of the amino-acids taurine, aspartic acid, isoleucine, histidine and arginine, but in patients with hepatolenticular degeneration there are persistently increased amounts of these amino-acids, plus proline, citrulline and a group of dicarboxylic peptides which are never found in normal urines. The urinary pattern is not a constant one, but rather varies from day to day, depending upon the amount and type of protein ingested and other as yet unknown factors. Significantly, there is no correlation between the degree of amino-aciduria and the severity of the hepatic disease, nor is there any elevation in the blood alpha amino-nitrogen level. The copper spillage rather appears to be related to a specific defect in renal tubular absorption, perhaps secondary to tubular injury (in the form of respiratory enzyme inhibition) produced by the elevated tubular copper level.

Copper is a powerful inhibitor of oxidative enzymes even in highly dilute solution. Lipman found that a copper concentration of 0.636 milligrams per cent inhibited glycolysis by muscle tissue. In a patient with Wilson's disease Glazebrook found that the copper concentration in the basal ganglia was of the order of 1.28 milligrams per cent, i.e., twice the concentration necessary to produce an histotoxic anoxia and tissue necrosis.

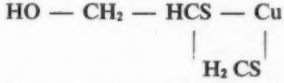
There is then a highly distinctive biochemical picture in Wilson's disease, characterized by a low serum copper, increased tissue copper, increased urinary copper, and amino-aciduria. This urinary picture is found only in Wilson's disease and in the nephrotic

syndrome—a disease which is also associated with renal tubular injury.

It has been suggested that the basic defect in hepatolenticular degeneration is an inability to synthesize ceruloplasmin, as a result of which the serum is saturated with copper at a low concentration. This low concentration is responsible in some unknown manner for increased gastro-intestinal absorption of copper which is then deposited in increased amounts in the brain, liver and kidney, producing the pathologic and pathophysiologic picture of the disease by virtue of the toxic effect of the increased tissue concentration of this ion.

TREATMENT

If this pathogenetic formulation is accepted, any definitive therapeutic measures should be directed at lowering the tissue copper level or, more basically, increasing the serum ceruloplasmin. Many workers have made attempts to do this by the administration of BAL which binds copper as



by use of chelating agents such as versene, by the use of potassium sulfide to bind the ingested copper as copper sulfide, and by the use of high protein diets in an attempt to increase the urinary loss of copper, thus producing a negative copper balance. Crystalline ceruloplasmin is available for experimental purposes, but has not been adequately evaluated.

The results of such therapeutic measures have been difficult to evaluate with some patients showing remarkable improvement as manifested by a decrease in the Kayser-Fleischer ring, decreased tremor and rigidity. The improvement has lasted from several weeks to a year. Other patients, however, have shown little or no improvement. Considering the pathological changes in the disease, these findings are perhaps as would be expected. The true value of these therapeutic measures will become apparent only when many minimal cases have been treated, and even then it will be exceedingly difficult to evaluate the results because of the chronic and variable course of the disease. One early case has been treated by the use of the above measures for approximately four years and has shown no progression during this period.[3]

HEPATIC ENCEPHALOPATHY

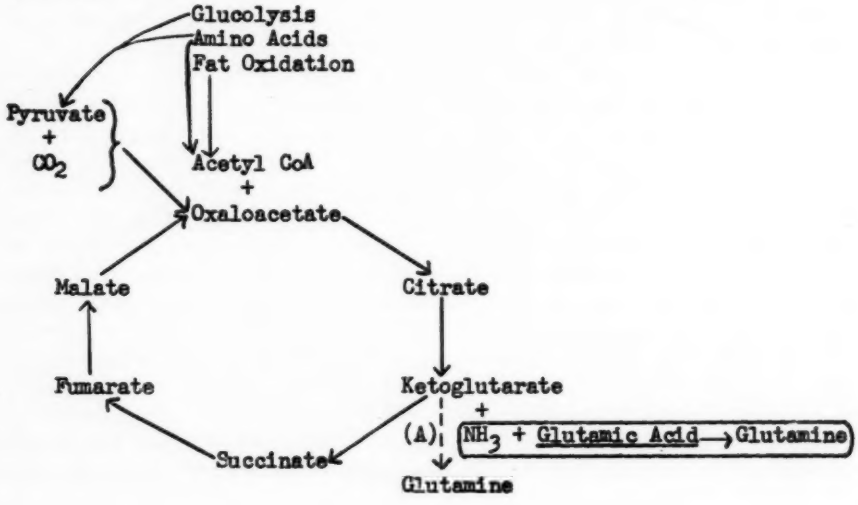
A second particularly fruitful field of research involving the relationship between hepatic and neurological disease has been the investigation of the etiology of hepatic coma. Historically, the study extends back for 60 years to 1893, when Pavlov described a syndrome in dogs which he called "meat intoxication."[1] He was able to repeatedly induce a state of confusion and coma in dogs with Eck fistulas by feeding them meat. This remained an isolated observation and no further work was reported in this field until 1932, when Van Caulaert showed that the ingestion of ammonium chloride by cirrhotics produced the picture of hepatic encephalopathy.[2] In 1934 Krauss related these two observations by demonstrating that the syndrome of meat intoxication described by Pavlov was associated with an elevated blood ammonium.[3] He postulated that the basic defect was an inability of cirrhotics to utilize ammonium in the synthesis of urea. However, in 1936 Kirk showed that cirrhotics had no disturbance in urea synthesis and he suggested that ammonium and/or meat intoxication was the result of direct absorption of nitrogenous substances into the peripheral circulation by virtue of the circulatory shunt

around the liver in the Eck fistula animal or in the cirrhotic.[4] For some strange reason, little further work was done until 1952, when Davidson using three patients with Laennec's cirrhosis, was able to consistently induce encephalopthy by feeding them nitrogenous substances.[5] Extending this work in 1954 McDermott put one patient who had a portacaval shunt on a virtual merry-go-round, inducing eight episodes of stupor by feeding the patient protein, urea, ammonium chloride and ammonium resins.[6] In this one patient he found a consistent correlation between the clinical state and the blood ammonium level, but in his other patients he found only a suggestively positive correlation with many individual exceptions. Neurologically the patient showed confusion, clouding of consciousness, grasping and sucking reflexes, the flapping tremor that was described in connection with Wilson's disease, and finally coma. The electroencephalographic changes consisted primarily of bilateral synchronous slow waves from the frontal areas.

The failure of many individual cases to show a positive correlation between the venous ammonium level and the clinical picture remained a mystery until late 1955, when Bessman studied the arterial ammonium concentration in a group of patients with hepatic disease.[7] In this group of patients the arterial level was often definitely elevated while the venous level would be normal or only slightly elevated, and in one patient who was in hepatic coma, there was a definite correlation between the arterial ammonium concentration and the clinical state although the patient maintained an essentially normal venous concentration of ammonium throughout. He also showed that muscle utilizes approximately 40 per cent of the ammonium reaching it while brain tissue utilizes only 20 per cent. Since the muscle mass is far greater than the brain cell mass and since muscle utilizes twice as much ammonium, the mixed peripheral venous ammonium concentration may well be normal while cerebral venous and arterial concentrations are moderately elevated.

PATHOGENESIS

Muscle tissue and brain are thought to utilize ammonium by the same biochemical pathway—the Krebs cycle.



When the arterial ammonium concentration is increased, the side reaction (A) is increased with a resultant decrease in the alpha ketoglutaric acid concentration and consequent slowing of the cycle. Replacement of any of the intermediates should restore the cycle. As can be seen from the diagram, there are several potential methods by which the essential intermediates might be replaced. Brain cells, however, are impermeable to amino acids with one important exception—glutamic acid. Thus there can be no direct replacement of any of the reactants in Krebs cycle. The reaction pyruvate plus carbon dioxide to oxaloacetate can occur only in the liver and cardiac muscle because of the absence of necessary enzymes elsewhere. Thus this reaction is also not available to brain cells. Oxidative deamination of aspartic acid to oxaloacetate could theoretically occur but does not actually do so, again because of the impermeability of the brain cells to amino acids. Muscle tissue, on the other hand, can utilize all of these methods. The brain is thus extremely limited in its ability to replenish the consistuents of the Krebs cycle.

Krebs in 1935 made an important and fundamental observation when he showed that in the presence of adequate amounts of glucose, brain slices can synthesize glutamine from glutamic acid and ammonium, and that this reaction occurs in a preferential fashion.[8] This observation provides the rationale for the utilization of glutamic acid in the treatment of ammonium intoxication since, as is apparent from the diagram, glutamic serves to prevent the side reaction (A) from occurring and thus protects the Krebs cycle.

Considerable amounts of ingested nitrogenous substances are broken down in the gastrointestinal tract to yield free ammonium which is then absorbed. In a normal person this absorbed ammonium is metabolized in the liver while in patients with hepatic disease, this protective mechanism is lacking either as a result of specific liver cell failure and/or the result of collateral circulation. Sherlock attempted to define the role of impaired liver function and of collateral circulation in the production of the picture of hepatic encephalopathy.[9] In a group of patients with viral hepatitis, the hepatic vein blood increased more after the ingestion of ammonium chloride than did the peripheral blood, suggesting that ammonium passed directly through the liver without undergoing any metabolic transformation. On the other hand, a group of advanced cirrhotics with extensive collateral circulation showed the reverse situation, that is, the peripheral blood ammonium concentration increased considerably more than did the hepatic vein concentration, suggesting that both functional impairment and circulatory shunts are important in the production of hepatic coma; the relative importance of each varying with the underlying hepatic pathology.

An interesting but as yet unexplained observation is that patients with Banti's syndrome, who have marked collateral circulation around their livers, allegedly do not show cerebral symptoms. I have not, however, been able to find any report of blood ammonuim levels in such patients.

TREATMENT

Numerous papers have appeared since Walshe's original report of the successful treatment of four out of five episodes of hepatic coma in three patients in 1953.[10] The results have been conflicting, and often directly contradictory, but much of the confusion may be cleared by the adoption of the classification suggested by Eiseman and McDermott who have proposed that the patients be divided into three groups accord-

ing to the mode of onset of the encephalopthy. They typify the patients as spontaneous, induced and chronic examples of encephalopthy. In the spontaneous group they include those patients who, without obvious precipitating factors, pass rapidly into hepatic encephalopathy with a rapid progression of symptoms. In the induced group they include those patients who have fallen into coma as the result of some usually obvious precipitation factor such as hemorrhage, large ingestion of protein, or ingestion of ammonium. In the chronic group they include those patients who show long standing evidences of encephalopathy without definite progression of the symptoms and without any obvious precipitating factors. In McDermott's series of 28 patients treated with L glutamic acid the results were as follows: (11)

		Cases	Fall In NH_4	Improved Clinically	Normal Clinically
I	Spontaneous	6	4	2	0
II	Induced	14	13	9	5
III	Chronic	8	7	7	6

Out of the 28 cases studied, 24 showed a fall in ammonium concentration after the administration of glutamic acid, and nine of those with induced encephalopathy showed improvement clinically with five returning to a normal status. In the chronic group, seven of the eight improved clinically and six were felt to return to normal status. As can be seen, the results in the spontaneous group are poor.

The conclusions which they reached are that ammonium intoxication is a specific form of exogenous encephalopathy which is reversible within limits by glutamic acid, but that in the spontaneous, and probably in the chronic cases, there are other as yet unknown, but undoubtedly complex, chemical changes which do not respond to glutamic acid administration. Their conclusions and their classification probably best summarize the whole problem of therapy at the present time.

SUMMARY

Although the therapeutic benefits derived from these investigations are not as dramatic as might be desired, the results do give us some idea of the success to be expected from the continued application of biochemical methods to the study of neurological diseases which are presently of an obscure etiology.

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THE BREVITY OF BABINSKI

J. DeWitt Fox, M.D.*

If you'd like to launch yourself into immortality, probably the brevity formula of Babinski is the best plan. The "big toe" sign known to every medical student and physician the world over was first described by M. Joseph Babinski in 1896 in *one short page*.

Just a paragraph or two at the bottom of page 207 carrying to top of 208 in the *Comptes Rendus de la Societe de Biologie*[1] did it. In a follow-up of a two-page article two years later in *Semaine Medicale*,[2] Babinski elaborated a bit, describing fully the appearance of dorsiflexion of the great toe in pyramidal tract diseases, and pointed out that it was also present in infants, in whom the pyramidal tract has not yet developed.

An open-eyed physician who boils down his observations is likely to hit the mark squarely. Next time you scratch a foot and elicit the Babinski sign, remember the beauty of Babinski's brevity and the place it won him in immortality; which bears out the old adage: "He who thinketh by the inch and speaketh by the yard ought to be kicketh by the foot."

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*Resident, Division of Neurosurgery

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INTRODUCTION TO NEW STAFF PERSONNEL

GERALD FINE, M.D., joined our Pathology Staff on April 16, 1956. He is a native of St. Paul, Minnesota, and is 32 years of age. He graduated from the University of Minnesota in 1943 and received his M.D. degree from the same school in 1946. He interned at St. Francis Hospital in LaCrosse, Wisconsin, and took 2 years of Pathology Residency at the Research and Educational Hospital in Chicago. Dr. Fine then spent 2 years in the United States Navy Medical Corps. He then spent 2½ years on the Pathology Staff at Francis Delafield Hospital in New York. He is married and resides at 3227 Albert Ave. in Royal Oak.

BOY FRAME, M.D., joined our staff in General Medicine on January 12, 1956. He is a native of Shenandoah, Iowa, and is 33 years of age. He graduated from Yale University in 1944 and received his M.D. degree from the same school in 1948. He interned at Massachusetts General Hospital, Boston, in 1949. He took his residency training in Internal Medicine at Yale University Hospital (1 year), Massachusetts General Hospital (2 years), and the Neurological Institute in New York (1 year). He then spent 2 years as an Internist in the United States Army Air Force. He is married with 1 child and resides at 1051 Covington Drive in Detroit.

WILLIAM C. SCHAEFER, M.D., joined our staff in Physical Medicine and Rehabilitation on January 30, 1956. He is a native of Pittsburgh, and is 41 years of age. He graduated in 1936 from the University of Pittsburgh and received his M.D. degree from the same school in 1939. He interned at Allegheny General Hospital in Pittsburgh and then spent 5 years in the United States Army Medical Corps. Following this Dr. Schaefer took 2 years of Anesthesiology Residency at Hartford Hospital, Hartford, Connecticut. In 1948 he was an instructor in Anesthesiology at Georgetown Medical School. In 1949 he was Chief of Anesthesiology at Gallinger Hospital in Washington, D.C., and the following year he held the same post at Alexandria Hospital, in Alexandria, Virginia. Dr. Schaefer then spent 3 years in the private practice of Anesthesiology in Evansville, Indiana. He then took a Fellowship in the United States Public Health Service at New York Bellevue Hospital, Department of Physical Medicine and Rehabilitation, and the following year he continued this training at the Mayo Clinic. In 1954 he was Chief of Physical Medicine and Rehabilitation at the VA Hospital in Indianapolis. Last year he was in private practice in Evansville, Indiana, and acted as Consultant in Physical Medicine and Rehabilitation at the Good Samaritan Hospital in Vincennes, Indiana. He is a member of the American Congress of Physical Medicine and Rehabilitation. He is married with 2 children and resides at 14634 Warwick Road.

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

TISSUE COENZYME A IN NORMAL AND INDUCED STATES OF GROWTH. P. D. Bartlett, P. Grimmett, L. Beers and S. Shelata. J. Biol. Chem. 218:419, 1956.

Results of studies from other laboratories on the pantothenic acid requirement of normal adult and rapidly growing immature rats, as well as studies on the effects of growth hormone in pantothentic acid deficient rats, suggest that either pantothenic acid or its metabolically active form, coezyme A, might be involved in the mechanism by which growth hormone stimulates the growth process. In this connection we have determined coezyme A concentration in kidney and liver tissue obtained from rats in both normal and induced states of growth, and also in rats in which the growth process has been arrested either by hypophysectomy of the immature animal or by the attainment of the adult state. Concentrations of liver coezyme A were found to be significantly lower in both hypophysectomized immature and normal adult rats than in rapidly growing immature normal rats. Induction of nitrogen storage and gain in body weight in the normal adult rat as a result of stimulation with growth hormone was accompanied by a significant elevation in the concentration of liver coenzyme A. Stimulation of the growth process in the hypophysectomized rat with growth hormone, however, failed to significantly alter the level of liver coenzyme A. Concentrations of kidney coenzyme A were not significantly altered in any case. There appears to be a direct relationship between liver coenzyme A concentrations and growth in the normal rat.

RESPIRATORY IRREGULARITIES IN NEWBORN INFANTS. A. R. Bauer and P. J. Howard. Postgrad. Med. 19:161, 1956.

Study of the respiration of the newborn infant has shown irregularities of rate, rhythm and amplitude. A body plethysmograph has been used in this investigation, and a classification of the types of irregularity is offered. The effect of low and high oxygen respiratory mixtures was studied, and led respectively to depression and stimulation. Carbon dioxide respiratory mixtures were shown to be strong stimulants. Irregularity in phase of expansion and contraction was found between chest and abdomen. Administration of 40 per-cent oxygen in the respiratory mixtures gave practically as much stimulation as higher mixtures. This is becoming a matter of great importance, for evidence is accumulating rapidly to indicate that toxic results of oxygen administration, such as retrolental fibroplasia and pulmonary irritation, occur from concentrations higher than 40 to 50 per cent.

EFFECTS OF B-SITOSTEROL AND FERRIC CHLORIDE ON ACCUMULATION OF CHOLESTEROL IN MOUSE LIVER. W. T. Beher and W. L. Anthony. Proc. Soc. Exper. Biol. & Med. 90:223, 1955.

Experimental studies were made on the influence of B-sitosterol and ferric chloride on liver cholesterol accumulation in mice fed diets rich in cholesterol. The mice were divided into several groups, each group receiving diets containing varying amounts of

cholic acid, B-sitosterol and ferric chloride. Four groups received increasing amounts of cholic acid: 0, 0.25%, 0.5%, and 1%. Cholesterol assay showed that increasing dietary cholic acid significantly increased total liver cholesterol — 10.6 mg., 36.1 mg., 47.1 mg. and 48.0 mg. per liver respectively. Another three groups received diets with the same proportions of cholic acid supplemented with 2.5% of B-sitosterol. B-sitosterol was effective in preventing the accumulation of total liver cholesterol. Total cholesterol per liver was: 10.6 mg., 30.0 mg., 24.9 mg., and 34.2 mg. respectively. In the third part of this experiment, the effect of ferric chloride on accumulation of liver cholesterol was studied. While the concentrations of cholesterol and cholic acid were maintained constant at 1% and 0.5% respectively, increasing amounts of ferric chloride were added to the diets. The percentages of iron added were: 0, 0.05%, 0.5%, 1.0%, and 2.0%. The assay of liver cholesterol showed no change in total cholesterol content of mouse liver.

ACETYLCHOLINESTERASE ACTIVITY IN THE COCHLEA. J. A. CHURCHILL, H. F. SCHUKNECHT AND R. DORAN. Laryngoscope 66:1, 1956.

There is an unique nerve bundle arising from cells near the olivary nucleus which passes across the medulla to end somewhere in the contralateral cochlea. The ending of this tract has not yet been determined, and little of its function is understood. If these nerve endings were cholinergic in nature, they might be located by applying Koelle's method for acetylcholinesterase. Furthermore it was worthwhile to determine whether or not acetylcholinesterase was present in the cochlea. The ultimate problem is to determine whether the enzyme is related to the hair cells, afferent endings of the acoustic nerve, or to terminals of the olivar-cochlear bundle. Should it be related to the afferent structures, support is lent to the hypothesis of Derbyshire and Davis that there exists a chemical mediator of excitation in the cochlea. Koelle's histochemical method involves incubating tissue samples in a solution containing acetylthiocholine and cupric ions. The substrate is hydrolyzed by the enzyme, as acetylcholine would be, and the thiocholine released by hydrolysis is precipitated by the cupric ion as copperthiocholine. Later the location of this compound is visualized by developing the tissues in ammonium sulphide which produces copper sulphide, a black insoluble precipitate. All cochleae treated revealed strong indications of acetylcholinesterase activity near the hair cells in the organ of Corti. Some nerve fibers were also stained.

TIME-DOSE RELATIONSHIPS. LUCILLE A. DUSAULT. Am. J. Roentgenol. 75:597, 1956.

The time during which radiation is delivered can effect the response to the dose given. There are three aspects of time to be considered: r/min., or the rate at which each treatment is given, the overall time of the series or the time from the beginning of the first treatment until the end of the last, and the degree of fractionation or spacing of the individual treatments. Within the limits commonly used in radiotherapy the first seems to be unimportant. When treatments are given fairly close together, for example daily, the effect is dependent only on the overall time within wide limits. By proper timing of the individual treatments the effect may be either increased or decreased. Plant and animal experiments on the effect of time are cited, and curves based on clinical results in patients are given for iso-effect lines for different tissues and reactions, showing the relationship between dose and time. It is suggested that further

study of the effect of fractionation might yield information which would result in improvement of therapy techniques by increasing the differential effect between tumor and normal tissue.

EXTRAINTESTINAL ROENTGEN MANIFESTATIONS OF INTESTINAL LIPODYSTROPHY. W. R. Eyler and H. P. Doub. J. A. M. A. 160:534, 1956.

Intestinal lipodystrophy is manifested in various gastrointestinal symptoms and in characteristic roentgen findings. The barium pattern in the small intestine is one of mucosal coarseness and flocculation or clumping with discontinuity of the column. In addition, certain extraintestinal manifestations aid in making the diagnosis. These are well illustrated in the four cases described. In each instance, the intestinal manifestations were typical. The extraintestinal manifestations included enlargement of mediastinal, retroperitoneal, or peripheral lymph nodes; narrowing of the hip joints; and arthritic changes in the sacroiliac joints. A widening of the duodenal loop observed in one patient was ascribed to pressure from a mass of enlarged retroperitoneal lymph nodes. Patients in whom the symptoms and intestinal roentgen findings suggest lipodystrophy should have further roentgen studies of the duodenal loop, the chest, and the sacroiliac joints.

MALIGNANT ARGENTAFFINOMA ASSOCIATED WITH CARDIOVASCULAR ABNORMALITIES. W. R. Eyler, H. Tesluk and E. H. Drake. New England J. Med. 254:555, 1956.

A case of malignant argentaffin tumor with an increase in facial telangiectasia and cyanosis, as well as the development of the murmurs of tricuspid insufficiency and pulmonic stenosis during observation, is presented. Progressive enlargement of the right atrium and ventricle was shown by x-ray study and fluoroscopy. Angiocardiography confirmed the diagnosis of pulmonary stenosis of the valvular type. Cardiac catheterization excluded a shunt and indicated the valvular lesion.

OCULAR MOVEMENT: I. MECHANICS, PATHOGENESIS AND SURGICAL TREATMENT OF ALTERNATING HYPERTROPIA (Dissociated Vertical Divergence, "Double Hyper") AND SOME RELATED PHENOMENA. Jack S. Guyton and Neil Kirkman. Am. J. Ophthal. 41:438, 1956.

Alternating hypertropia, wherein the left eye deviates upward while the right eye is fixating and the right eye deviates upward while the left eye is fixating, has always constituted a puzzling and apparently paradoxical phenomenon. Alternating hypertropia is quite common in cases of squint, and it long has been known to impart a poor prognosis for single binocular vision. Nevertheless, its pathogenesis and physiologic mechanics have remained an enigma, and no surgical treatment has been recommended other than correction of any concurrent horizontal deviation. Proof is offered of two theorems which lead to an explanation of alternating hypertropia. These theorems state, in brief: (1) Fixation of an eye on a traget, either binocularly or with either eye separately, demands the fixating positions of the two globes relative to any given postural position of the head must be exactly equivalent in all three rotational compcnents for proper (subjectively equivalent) spatial orientation. That is, not only must the horizontal and vertical rotation components of each eye be such as to point the

visual axes in equivalent directions toward the target, but also the torsional components of rotational position must be such as to place corresponding retinal meridians into equivalent positions. (2) A change in conjugately applied motor stimulation which will move the right eye from an initial position Ra into position Ra+b should *not* move the left eye from a different initial position Lc *exactly* into position Lc+b. Utilizing extensions of the above two theorems, it is shown that the alternate vertical deviations of alternating hypertropia are merely the vertical components which should be expected, on alternate fixation, from deviations which have qualitatively "commitant" torsional components. Subjecting the theory to practical test, surgical correction of underlying torsional deviations effectively stops the alternating vertical deviations. Surgical corrections of this nature, the planning of which is given in detail, appear quite important to the attainment of binocular vision in a large class of squints.

THE ROLLER TUBE TISSUE CULTURE TECHNIQUE IN THE EVALUATION OF THE PRIMARY IRRITANCY PRODUCING CAPACITY OF TOPICAL MEDICAMENTS AND CHEMICALS. F. HU, C. S. LIVINGOOD AND J. HILDEBRAND. J. Invest. Dermat. 26:23, 1956.

A laboratory method is described for the determination of the potential irritancy-producing capacity of various medicaments (and certain chemicals) used in the topical treatment of skin diseases. The circumcised foreskin from infants was cultivated with the use of the roller tube tissue culture technique. The culture medium consisted of a plasma-embryonic extract clot and a fluid nutrient of balaced salt solution, embryonic extract and malignant ascitic fluid. Pieces of skin were explanted in the clot on a 12 x 50 mm. No. 1 coverslip which was then placed in a test tube with 2 ml. of nutrient fluid. The tube was stoppered and incubated at 37° C. in a roller drum which rotated at a speed of 12 revolutions per hour. Epithelial outgrowth in sheets usually began to appear in five to six days and continued to increase in size up to three to four weeks. Usually, a sheet of epithelial cells about the diameter of the original explant was obtained evenly around the explant after cultivation for ten to fourteen days. The drugs to be tested were incorporated into the cultures at this time; the time of contact with the epithelial cells was 18 or 42 hours. The toxic effects were determined by comparing the controls and test cultures at the end of the period of exposure. The signs of injury were manifested by changes in cellular characteristics — pyknosis of nuclei, karyorrhexis, and loss of cell outline. In some, after the epithelial sheets were in contact with the drug for 18 or 42 hours, the supernatant which contained the test substance was removed and fresh nutrient was reintroduced. These cultures were kept for another week to determine the capacity of the cultures to recover after exposure to the drugs or chemicals was discontinued.

Drugs tested in this study included various antibiotics, topical anesthetic agents, antihistaminics, and other topical therapeutic medicaments; also certain chemicals were studied. The correlation of results obtained with this issue culture roller tube technique and clinical experience, including patch tests, seems to be of a sufficient degree of accuracy to justify the conclusion that this method has a place in the preclinical evaluation of new topical medicaments. Also, this approach has a possible application in determining the potential toxicity for skin and mucous membranes of new chemicals used in industry.

STUDIES IN RHEUMATIC FEVER. J. A. JOHNSTON. A. M. A. J. Dis. Child. 91:250, 1956.

1. *Nutrition as a factor conditioning its incidence and course.*

From a 25-year experience with rheumatic fever in the Henry Ford Hospital it is concluded that the ultimate outcome as judged by mortality and the occurrence of carditis is conditioned by the nutritional state of the child in his first attack. Valid statistical correlations were established between the ultimate outcome and (1) the child's position on the Wetzel grid; (2) his past history of diet with particular reference to protein. Inferences of previous deficits in the nitrogen pool were obtained by nitrogen balance studies showing large recovery gains of this substance with flat weight curves.

2. *The experience since the advent of corticotropin and cortisone.*

The end results of treatment of 76 cases since 1949 show a highly significant improvement over those recorded in 270 cases seen before 1949. This cannot be adduced as clear-cut evidence in favor of hormone treatment since (1) we have combined cortisone and salicylates, and (2) there is general agreement that there has been a decline in the severity of the disease. If, however, our basic thesis noted in the first section is correct — namely, that anything influencing favorably the nutritional state has a beneficial effect on outcome — then the studies strongly favor the use of cortisone. With salicylates alone we noted no increase in intake or storage of nitrogen; with cortisone, following initial increases in urinary loss, large gains of nitrogen follow the increased intake commonly seen and the net result in the addition to the body of large increments of nitrogen.

3. *Effect of activity and rest on the nutritional state in rheumatic fever.*

The prolonged inactivity commonly imposed in rheumatic fever carries with it, after the temperature and pulse have become normal, the adverse effects of the metabolism of disuse — failure to retain nitrogen and calcium. It is shown that these can be simply offset by moderate activity not sufficient to cause an elevation of pulse or pulse pressure. Amounts causing these changes were accompanied by a fall in nitrogen storage though a continued rise in calcium retention.

BILATERAL ADOLESCENT MAMMOPATHY AS A PRESENTING SYMPTOM OF RHABDOMYOSARCOMA OF THE HEART. G. MANSON AND W. RINDSKOFF. J. Pediat. 48:202, 1956.

Rhabdomyosarcoma of the heart is a rare pathologic condition. When bilateral tumors of the breast are the presenting complaint of such a condition and this is followed shortly by evidence of widespread bony involvement, a bizarre and puzzling picture results. It was felt that the occurrence of a case combining these unusual features merited reporting. This is the nineteenth case of primary rhabdomyosarcoma of the heart together with autopsy findings. The differential diagnosis of bilateral adolescent breast masses includes: virginal hypertrophy of the breast, benign fibroadenoma, non-indigenous breast lesions (fatty, angiomatous, myomatous, cartilaginous and osseous tumors, dermoids, sweat gland tumors both benign and malignant), extra mammary tumors, metastatic to the breast with a final diagnostic consideration. The reasons for considering this tumor primary in the heart a rare site of origin are enumerated, together with a brief review of the literature.

STUDIES OF THE ADRENAL HYPERFUNCTION IN 2 PATIENTS WITH ATYPICAL CUSHING'S SYNDROME. R. C. MELLINGER AND R. W. SMITH, JR. J. Clin. Endocrinol. & Metab. 16:350, 1956.

Case studies of two patients with adrenocortical hyperplasia have been reported. Both patients presented a clinical syndrome of marked atrophy of the bones, muscle and skin without other features commonly observed in Cushing's syndrome. It is postulated that the adrenocortical hyperfunction in these cases was characterized by excessive 17-hydroxycorticoid excretion with either a relative or an absolute decrease in protein-anabolic adrenal steroids. Although the urinary 17-hydroxycorticoid level was elevated in both patients, the metabolic derangement was more clearly demonstrated by the 17-hydroxycorticoid-creatinine ratio (steroid index). Both patients responded to small doses of ACTH with marked increases in 17-hydroxycorticoid excretion. This increased sensitivity of the adrenal cortex is interpreted to mean that endogenous ACTH levels are normal or low in these cases, and that the primary derangement is in the adrenal cortex. In another patient with pituitary basophilism, on the other hand, the adrenocortical hyperfunction was considered secondary to increased ACTH elaboration, and the response to administered ACTH was no greater than normal. Both patients of this report underwent bilateral total adrenalectomy successfully. Adrenocortical hyperplasia was the pathologic finding in both cases.

*REMOTE TONGS ADAPTED FOR THE SMALL RADIOISOTOPE LABORATORY. L. PREUSS. Nucleonics 14:79, 1956.

The alteration of two remote control tongs designed for usage in the small radioactive isotope laboratory is described. The basic mechanism is obtained from two commercially available extension cutters. This custom tong construction is rapid, convenient, and well adapted to the needs and budget of the small laboratory.

*VACUUM CRUCIBLE VIEWING METHOD. L. E. PREUSS. Rev. Scientific Inst. 27:61, 1956.

A conventional 3" x 1" glass slide (for a reflector) is positioned with a grey non-reflecting backing, 4 to 8 cm. from the crucible. The backing may be produced by about 5000 angstroms of chromium condensed on a slide or brass plate. A small space between the slide and this background improves the function of the reflector. The mirrored images of the crucible and charge are sighted in the slide by the unprotected eye at a small incidence angle. A shield may be set up to protect the eye from the direct glare. Depending upon the viewing angle, the reflected image will be of varying intensity and the usual painful glare is eliminated. Varying the thickness of the metal film deposited on the wall of the bell jar may also be an adjunct to the procedure. An appropriate combination of absorber film thickness and viewing angle is chosen for a comfortable intensity to the eye. The technique may be used throughout the evaporation procedure until the slide condenses a heavy metal layer. This may be minimized by placing the glass plate in an area with a low evaporant dispersion rate for the particular crucible used.

*From Edsel B. Ford Institute for Medical Research.

PHENOXYMETHYL PENICILLIN (Penicillin V) THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS. E. L. QUINN, J. M. COLVILLE, F. COX, JR. AND J. TRUANT. J. A. M. A. 160:931, 1956.

Penicillin V was compared with penicillin G as to the concentrations attained in the blood when the two antibiotics were taken by mouth. In eight normal fasting subjects the average serum concentrations showed that penicillin G was absorbed faster and reached a higher concentration during the first half-hour, but thereafter penicillin V reached concentrations 1.7 to 2.8 times as high as those of penicillin G, and this difference was found consistently at the end of the first, second, third, and fourth hours. Penicillin V also gave higher blood concentrations than did penicillin G when given to four patients orally at four-hour intervals over a period of weeks. Case histories of two patients with bacteremia caused by alpha-hemolytic streptococci illustrated the effectiveness of orally administered penicillin V in bringing about a sustained clinical remission. A third patient, whose bacteremia was caused by Neisseria sicca, obtained clinical and bacteriological remission for a course consisting of 2 million units of penicillin V orally every four hours with 0.5 gm. each of streptomycin and dihydrostreptomycin intramuscularly twice daily. In a fourth patient, bacteremia caused by a Micrococcus pyogenes was halted but temporarily, and at the time of relapse the organism was found exceptionally resistant to antibiotics.

CELLULAR STRUCTURE, FUNCTION AND RELATIONS IN ANTIBODY FORMING LYMPH NODES. J. W. REBUCK, T. N. HARRIS AND S. HARRIS. Anat. Rec. 124:351, 1956.

Abstract of a paper presented at the sixty-ninth annual session of the American Association of Anatomists, Milwaukee, Wis., April 4-6, 1956.

SURGICAL SIGNIFICANCE OF MARJOLIN'S ULCER WITH A REPORT OF THREE CASES. R. J. SCHLOSSER, E. A. KANAR, AND H. N. HARKINS. Surgery 39:645, 1956.

Marjolin's ulcer is a cancer arising in a burn scar. About 2.0 per cent of burn scars will develop a squamous-cell and 0.3 per cent, a basal-cell carcinoma. Marjolin's ulcer is seen most commonly in the male despite the greater frequency of burns in young women. In contrast to the site of origin of the ordinary skin cancer, it occurs most frequently on an extremity. Moreover, the age of a burn scar has greater significance in the development of a burn scar cancer than the age of the patient. An old extremity scar of an adult burned as an infant or child will more readily terminate in a Marjolin's ulcer than the scar of burns more recently sustained as an adult. The exception arises only in the elderly patient whose senile skin is more susceptible to carcinogenic influences, such as a burn, than the normal skin of a younger person. Virchow's concept of the irritative origin of scar cancer is briefly discussed in relationship to the etiology of Marjolin's ulcer. Reasons for the suggestion that biopsy of suspicious burn ulcers should include tissue from the base as well as from the margins are given. The treatment of Marjolin's ulcer is biphasic: 1. prophylactic-skin grafting of the burn defect is necessary initially and must be adequate; 2. definitive — the lesion must be widely excised surgically with or without lymph node dissection as indicated.